1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Retinoid for systemic treatment of acne.
ATC Code: D10BA01

1.2 Type of Dosage Form

Capsules: soft: 10 mg and 20 mg.

1.3 Route of Administration

Oral
.

1.4 Qualitative and Quantitative Composition

Active ingredient: isotretinoin; 13-*cis* retinoic acid.
Excipients:
Capsule filling:
Beeswax, yellow;
Soya-bean oil, refined;
Soya-bean oil, hydrogenated;
Soya-bean oil, partially hydrogenated.
Capsule shell:
Gelatin;
Glycerol 85%;
Karion 83 containing sorbitol, mannitol, hydrogenated hydrolysed starch;
Titanium dioxide (E171);
Red iron oxide (E172).
Dry printing ink:
Shellac, modified;
Black iron oxide (E172).

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Roaccutane is indicated for the treatment of severe forms of acne (nodular or conglobate acne, or acne at risk of permanent scarring) and acne which has failed to respond to standard therapies with systemic antibacterials and topical therapy.

2.2 Dosage and Administration

Roaccutane should only be prescribed by physicians who are experienced in the use of systemic retinoids and understand the risk of teratogenicity associated with isotretinoin therapy. Both female and male patients should be given a copy of the Patient Reminder Card (see sections 2.4 Warnings and Precautions and 2.5 Use in Special Populations).

The therapeutic response to Roaccutane and its adverse events are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy. Roaccutane therapy should be started at a dose of 0.5 mg/kg daily. For most patients the dose ranges from 0.5 to1.0 mg/kg per day. Patients with very severe disease or with truncal acne may require higher daily doses up to 2.0 mg/kg.

The capsules should be taken with food once or twice daily.

A cumulative treatment dose of 120–150 mg/kg per treatment has been documented to increase remission rates and prevent relapse. The therapy duration in individual patients therefore varies as a function of the daily dose. Complete remission of the acne is often achieved by a therapy course of 16–24 weeks. In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequence of a longer therapy duration.

In the majority of patients complete clearing of the acne is obtained with a single treatment course. In case of a definite relapse, a renewed course of Roaccutane therapy should be given with the same daily dose and cumulative treatment dose as previously. Since further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, retreatment should not be initiated until after this period.

2.2.1 Special Dosage Instructions

Renal impairment

In patients with severe renal insufficiency, Roaccutane treatment should be started at a lower dose (e.g. 10 mg/day). The dose should then be increased up to 1 mg/kg/day or until the patient is receiving the maximum tolerated dose (see section 2.5.5 Renal Impairment).

2.3 Contraindications

Roaccutane is contraindicated in:

Women of child-bearing potential

- Women of child-bearing potential unless the female patient meets all the conditions of the Pregnancy Prevention Programme (see section 2.4 Warnings and Precautions).

Pregnant or breastfeeding women

- Roaccutane is contraindicated in women who are pregnant or breastfeeding (see section 2.5 Use in Special Populations).

Tetracyclines

- Patients receiving concomitant treatment with tetracyclines (see section 2.4 Warnings and Precautions).

Hepatic insufficiency

- Patient with hepatic insufficiency (see section 2.4 Warnings and Precautions).

Hypervitaminosis A

- Patients with pre-existing hypervitaminosis A (see section 2.6 Undesirable Effects).

Elevated blood lipid values

- Patients with excessively elevated blood lipid values (see section 2.4 Warnings and Precautions).

Hypersensitivity

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

2.4 Warnings and Precautions

2.4.1 General

> ***Teratogenic effects***
> *Roaccutane is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects.*
> *Roaccutane is strictly contraindicated in:*
> - *Pregnant women*
> - *Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met*

Roaccutane is **TERATOGENIC.**

There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking oral Roaccutane in any amount even for short periods. Potentially all exposed fetuses can be affected.

Roaccutane is contraindicated in women of child-bearing potential unless the female patient meets all the conditions of the Pregnancy Prevention Programme.

The pregnancy prevention information should be given to the patients both orally and in writing.

Pregnancy Prevention Programme

Roaccutane is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:

- Roaccutane is indicated for the treatment of severe forms of acne (nodular or conglobate acne, or acne at risk of permanent scarring) and acne which has failed to respond to standard therapies with systemic antibacterials and topical therapy. (See Section Indication)
- The potential for pregnancy must be assessed for all female patients.
- She understands the teratogenic risk.

- She understands the need for frequent follow-up (e.g. on a monthly basis).
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the entire duration of treatment and for 1 month after the end of treatment. At least one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception should be used.
- Individual circumstances should be evaluated in each case, when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.
- Even if she has amenorrhea she must follow all the advice on effective contraception.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy or if she might be pregnant.
- She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and 1 month after stopping treatment.
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of Roaccutane.

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy. Even female patients who normally do not employ contraception because of a history of infertility (except in the case of hysterectomy) or who claim absence of sexual activity must be advised to use effective contraceptive measures while taking Roaccutane, following the above guidelines.

The prescriber must ensure that:

- The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.
- The patient understands that she must consistently and correctly use one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception, for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment.
- Negative pregnancy test results have been obtained before, during and 1 month after the end of treatment. The dates and results of pregnancy tests should be documented.

If pregnancy occurs in a woman treated with Roaccutane, treatment must be stopped and the patient should be referred to a physician specialized or experienced in teratology for evaluation and advice.

If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the fetus. The risk persists until the product has been completely eliminated, which is within one month following end of treatment.

Contraception

Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. If the prescribing physician is not in a position to provide such information the patient should be referred to the relevant healthcare professional.

A minimum requirement, female patients of child-bearing potential must use at least one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception. Contraception should be used for at least 1 month prior to starting treatment, throughout treatment and continue for at least 1 month after stopping treatment with Roaccutane, even in patients with amenorrhea.

Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

Pregnancy testing

- *Prior to starting therapy*
  At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a medically supervised pregnancy test. This test should ensure the patient is not pregnant when she starts treatment with Roaccutane.

- *Follow-up visits*
  Follow-up visits should be arranged at regular intervals, ideally monthly. Follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

- *End of treatment*
  1 month after stopping treatment, women should undergo a final pregnancy test.

Prescribing and dispensing restrictions

For women of childbearing potential, the prescription duration of Roaccutane ideally be limited to 30 days in order to support regular follow-up, including pregnancy testing and monitoring. Ideally, pregnancy testing, issuing a prescription and dispensing of Roaccutane should occur on the same day.

This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patient is not pregnant before receiving the next cycle of medication.

Male patients

The available data suggest that the level of maternal exposure from the semen of the patients receiving Roaccutane is not of a sufficient magnitude to be associated with the teratogenic effects of Roaccutane. Male patients should be reminded that they must not share their medication with anyone, particularly females.

Additional precautions

Microdosed progesterone preparations (minipills) may be an inadequate method of contraception during Roaccutane therapy.

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy and for 1 month following discontinuation of Roaccutane because of the potential risk to the fetus of a pregnant transfusion recipient.

Educational material

In order to assist healthcare professionals and patients in avoiding fetal exposure to Roaccutane, the Product Registration Holder will provide educational material to reinforce the warnings about the teratogenicity of Roaccutane, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

For physicians:
- Physician's Checklist/ Acknowledgement Form for Prescribing to Female Patients

For patients:
- Patient Reminder Card

For pharmacists:
- Pharmacist's Checklist- Guidance for Dispensing Roaccutane

Psychiatric symptoms
Depression, depression aggravated, anxiety, mood alterations and psychotic symptoms have been reported in patients treated with systemic retinoids. Particular care should be taken in patients with a history of depression. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Awareness by family or friends may be useful to detect mental health deterioration. Suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin. A causal relationship has not been established for these events.

Skin and subcutaneous tissue disorders
Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually within 7–10 days, and usually does not require dose adjustment.

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

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 the risk of hypertrophic scarring in atypical areas and more rarely hyper- or hypo-pigmentation in treated areas. Wax epilation should be avoided in patients on Roaccutane therapy and at least for a period of 6 months after treatment due to the possibility of epidermal stripping, scarring or dermatitis.

Concurrent administration of Roaccutane with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase.
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 [EM], Stevens-Johnson syndrome [SJS], and toxic epidermal necrolysis [TEN]) 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.

Eye disorders
Dry eyes, corneal opacities, decreased night vision, keratitis, blepharitis and conjunctivitis 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.

Decreased night vision has occurred during Roaccutane therapy and in rare instances has persisted after discontinuation of therapy (see section 2.6 Undesirable Effects). Because 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. Visual problems should be carefully monitored.

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 2.6 Undesirable Effects).

Bone changes, including premature epiphyseal closure, hyperostosis and calcifications of tendons and ligaments have occurred after several years of administration at high doses 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. Therefore, a careful evaluation of the risk/benefit ratio should be carried out in every patient.

Benign intracranial hypertension
Rare cases of benign intracranial hypertension “pseudotumor cerebri” have been reported, some of which involved concomitant use of tetracyclines (see section 2.4.3 Interactions with other Medicinal Products and other Forms of Interaction). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilledema. Patients who develop benign intracranial hypertension should discontinue Roaccutane immediately.

Therefore, concomitant treatment with tetracyclines should be avoided.

Hepatobiliary disorders
Liver function or enzymes should be checked before and 1 month after the start of treatment, and subsequently at 3 months 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, when transaminase levels exceed the normal levels, reduction of the dose or discontinuation of treatment may be necessary.

Lipid metabolism
Serum lipids (fasting value) should also be checked, 1 month after the start of therapy, and subsequently at 3 months intervals unless more frequent monitoring is clinically indicated. The serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment. The changes in serum lipids may also resolve in response to dietary measures.

It is recommended to control clinically significant serum triglyceride elevations, since levels in excess of 800 mg/dl or 9 mmol/l are sometimes associated with acute pancreatitis, which is known to be potentially fatal (see section 2.6 Undesirable Effects). Hence, Roaccutane should be discontinued if uncontrolled hypertriglyceridemia or symptoms of pancreatitis occur.

Gastrointestinal disorders
Roaccutane has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing 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.

High-risk patients
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.

In known or suspected diabetics, frequent determination of blood glucose levels is recommended. Elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during Roaccutane therapy.

2.4.2 Ability to Drive and Use Machines
Decreased night vision has occurred during and after discontinuation of Roaccutane therapy. Because 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 machine at night (see section 2.4 Warnings and Precautions).

2.5 Use in Special Populations
2.5.1 Females and Males of Reproductive Potential
Fertility
Isotretinoin, in therapeutic dosages, does not affect the number, motility and morphology of sperm and does not jeopardise the formation and development of the embryo on the part of the men taking isotretinoin. See section *3.3.3 Impairment of Fertility.*

Pregnancy Testing
Females of reproductive potential must undergo pregnancy testing before initiation of treatment with Roaccutane, during treatment and 5 weeks after the end of treatment. See section *2.4.1 Warnings and Precautions - Pregnancy Prevention Programme.*

Contraception
As Roaccutane is teratogenic, females of reproductive potential must comply with the Pregnancy Prevention Program. See section *2.4.1 Warnings and Precautions - Pregnancy Prevention Programme.*

Females of reproductive potential must use at least one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception. Contraception must be used for at least 1 month prior to starting treatment, throughout treatment, and continued for at least 1 month after stopping

treatment with Roaccutane, even in patients with amenorrhea. See section 2.*4.1 Warnings and Precautions - Pregnancy Prevention Programme.*

2.5.2 Pregnancy

Pregnancy is an absolute contraindication to treatment with Roaccutane. Women of child bearing potential should comply with the Pregnancy Prevention Programme. If pregnancy does occur during treatment with Roaccutane or within one month following treatment, there is a great risk of very severe and serious malformation of the fetus.

See section *2.3 Contraindications.*

Risks to the Developing Embryo/Foetus
The fetal malformations associated with exposure to Roaccutane include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality 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 should be referred to a physician specialised or experienced in teratology for evaluation and advice. See section *2.4.1 Warnings and Precautions - Pregnancy Prevention Programme.*

Labor and Delivery
Not Applicable

2.5.3 Lactation
As Roaccutane 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 nursing mothers.

2.5.4 Pediatric Use
The use of Roaccutane in pediatric patients less than 12 years of age has not been studied.

2.5.5 Renal Impairment
Severe renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Therefore, Roaccutane can be given to patients with renal insufficiency. However, it is recommended that patients are started on a low dose and titrated up to the maximum tolerated dose (see section 2.2.1 Special Dosage Instructions).

2.5.6 Hepatic Impairment
See section 2.4.1 Warnings and Precautions: General

2.6 Undesirable Effects
2.6.1 Clinical Trials
Summary of Safety Profile
Some of the side effects associated with the use of Roaccutane are dose-related. With the recommended dosage, the risk/benefit ratio is generally acceptable considering the severity of the disease. The side effects are generally reversible after altering the dose or discontinuation of treatment, however, some may persist after treatment has stopped.

The adverse reactions listed below reflect the experience from investigational studies of Roaccutane, and the post-marketing experience. The relationship of some of these events to Roaccutane therapy is unknown. Many of the side effects and adverse reactions seen in patients receiving Roaccutane are similar to those described in patients taking very high doses of vitamin A (dryness of the skin and mucous membranes, e.g. of the lips, nasal passage, and eyes).

Symptoms associated with hypervitaminosis A
The following symptoms are the most frequently reported undesirable effects with Roaccutane: dryness of the skin, dryness of the mucosa, e.g. of the lips, cheilitis, the nasal mucosa (epistaxis), 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.

Musculo-skeletal system disorders
Myalgia (muscle pain) with or without elevated serum CPK values (see section 2.4 Warnings and Precautions), arthralgia (joint pain), hyperostosis, arthritis, calcification of ligaments and tendons and other bone changes, reduced bone density, back pain, epiphyses, premature fusion tendinitis.

Psychiatric and central nervous system disorders
Behavioural disorders, depression (see section 2.4 Warnings and Precautions), suicide attempt, suicide, headache, increased intracranial pressure (pseudotumor cerebri), seizures. Although a causal relationship has not been established, particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary.

Sensory disorders
Isolated cases of visual disturbances, photophobia, dark-adaptation disturbances (decreased night vision), rarely colour vision disturbances (reversible upon discontinuation), lenticular cataract, keratitis, blurred vision, blepharitis, conjunctivitis, eye irritation, papilledema as sign of benign intracranial hypertension, impaired hearing at certain frequencies have been reported.

Gastro-intestinal 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 2.4 Warnings and Precautions).

Liver and biliary system disorders
Transient and reversible increases in liver transaminases, some cases of hepatitis.
In many such cases the changes have been within the normal range and values have returned to baseline levels during treatment. In other cases, however, it has been necessary to reduce the dose or discontinue treatment with Roaccutane.

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

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

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 2.4 Warnings and Precautions).

Resistance mechanism disorders
(Infections)
Local or systemic infections due to gram-positive microorganisms *(Staphylococcus aureus*)**.**

Miscellaneous reactions
Lymphadenopathy, hematuria, and proteinuria, vasculitis (for example Wegener's granulomatosis, allergic vasculitis), allergic responses, systemic hypersensitivity, glomerulonephritis.

2.6.2 Post Marketing Experience
During the post-marketing period, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with Roaccutane (see section 2.4 Warnings and Precautions).

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

2.7 Overdose
Signs of hypervitaminosis A could appear in cases of overdose. Evacuation of the stomach may be indicated in the first few hours after overdosage.

2.8 Interactions with other Medicinal Products and other Forms of Interaction

Concurrent therapy with Roaccutane and vitamin A must be avoided, as symptoms of hypervitaminosis A may be intensified.

Rare cases of benign intracranial hypertension “pseudotumor cerebri” have been reported, some of which involved concomitant use of tetracyclines. Therefore, concomitant treatment with tetracyclines should be avoided (see section 2.4 Warnings and Precautions.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Isotretinoin, the active ingredient of Roaccutane, is a stereoisomer of all-trans retinoic acid (tretinoin). The exact mechanism of action of Roaccutane has not yet been elucidated in detail, but it has been established that the improvement observed in the clinical picture of severe acne is associated with suppression of sebaceous-gland activity and a histologically demonstrated reduction in the size of the sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established.

3.1.2 Clinical / Efficacy Studies

Hypercornification of the epithelial lining of the pilosebaceous unit leads to shedding of corneocytes into the duct and blockage by keratin and excess sebum. This is followed by formation of a comedone and, eventually, inflammatory lesions. Roaccutane inhibits proliferation of sebocytes and appears to act in acne by re-setting the orderly programme of differentiation. Sebum is a major substrate for the growth of *Propionibacterium acnes* so that reduced sebum production inhibits bacterial colonisation of the duct.

3.2 Pharmacokinetic Properties

Since the kinetics of isotretinoin and its metabolites are linear, its plasma concentrations during therapy can be predicted from single dose data. This property also provides some evidence that the activity of hepatic drug metabolising enzymes is not induced by isotretinoin.

3.2.1 Absorption

The absorption of isotretinoin from the gastro-intestinal tract is variable; the absolute bioavailability of isotretinoin has not been determined, since the compound is not available as an intravenous preparation for human use, but extrapolation from dog studies would suggest a fairly low and variable systemic bioavailability. In acne patients at steady state, peak blood concentrations (C_{max}) of 310 ng/ml (range: 188–473 ng/ml) were observed 2–4 hours after dosing with 80 mg/day isotretinoin under fasting conditions. Plasma concentrations of isotretinoin are about 1.7 times those of blood concentrations due to poor penetration of isotretinoin into red blood cells.

When isotretinoin is taken with food, the bioavailability is doubled relative to fasting conditions.

3.2.2 Distribution

Isotretinoin is extensively bound to plasma proteins, mainly albumin (≥99.9%); therefore the free (= pharmacologically active) fraction of isotretinoin is less than 0.1% over a wide range of therapeutic concentrations.

The volume of distribution of isotretinoin in man has not been determined since isotretinoin is not available as an intravenous preparation for human use.

Steady-state blood concentrations ($C_{min, ss}$) of isotretinoin in patients with severe acne treated with 40 mg b.i.d. ranged from 120 to200 ng/ml; the concentration of 4-oxo-isotretinoin in these patients were 2–5 times higher than the isotretinoin concentrations. In humans little information is available on the distribution of isotretinoin into tissue. Concentrations of isotretinoin in the epidermis are only half of those in serum.

3.2.3 Metabolism

After oral administration of isotretinoin, three major metabolites have been identified in plasma: 4-oxo-isotretinoin, tretinoin (all-trans retinoic acid), and 4-oxo-tretinoin. The major metabolite is 4-oxo-isotretinoin with plasma concentrations at steady state, that are 2.5 times higher than those of the parent compound. Other minor metabolites have been detected but are not completely identified, which also includes glucuronide conjugates.

Isotretinoin metabolites have shown biological activity in several in vitrotests. Thus the observed clinical profile in patients could be the result of the pharmacological activity of isotretinoin and its metabolites.

Since isotretinoin and tretinoin (all-trans retinoic acid) are reversibly metabolised (= interconverted), the metabolism of tretinoin is linked with that of isotretinoin. It has been estimated that 20–30% of an isotretinoin dose is metabolised by isomerisation.

Enterohepatic circulation may play a significant role in the pharmacokinetics of isotretinoin in man.

In vitro metabolism studies have demonstrated that several CYP enzymes are involved in the metabolism of isotretinoin to 4-oxo-isotretinoin and tretinoin. No single isoform appears to have a predominant role. Roaccutane and its metabolites do not significantly affect CYP activity.

3.2.4 Elimination

After oral administration of radiolabelled isotretinoin approximately equal fractions of the dose were recovered in urine and feces. Following oral administration of isotretinoin, the terminal elimination half-life of unchanged drug in patients with acne has a mean value of 19 hours. The terminal elimination half-life of 4-oxo-isotretinoin is longer, with a mean value of 29 hours.

Isotretinoin is a physiological retinoid and endogenous retinoid concentrations are reached within approximately two weeks following the end of Roaccutane therapy.

3.2.5 Pharmacokinetics in Special Populations

Since Roaccutane is contraindicated in patients with hepatic impairment, limited information on the kinetics of Roaccutane is available in this patient population.

3.3 Nonclinical Safety

3.3.1 Carcinogenicity

Isotretinoin has not been shown to be carcinogenic in *in-vitro* or *in-vivo* animal tests.

3.3.2 Genotoxicity

Isotretinoin has not been shown to be mutagenic in *in-vitro* or *in-vivo* animal tests.

3.3.3 Impairment of Fertility

Isotretinoin, in therapeutic dosages, does not affect the number, motility and morphology of sperm and does not jeopardise the formation and development of the embryo on the part of the men taking isotretinoin.

3.3.4 Reproductive Toxicity

Like other vitamin A derivatives, isotretinoin has been shown in animal experiments to be teratogenic and embryotoxic.

Due to the teratogenic potential of isotretinoin there are therapeutic consequences for the administration to women of a child-bearing age (see sections 2.3 Contraindications, 2.4 Warnings and Precautions, and 2.5 Use in Special Populations).

3.3.5 Other

Acute toxicity

The acute oral toxicity of isotretinoin was determined in various animal species. LD50 is approximately 2000 mg/kg in rabbits, approximately 3000 mg/kg in mice, and over 4000 mg/kg in rats.

Chronic toxicity

A long-term study in rats over 2 years (isotretinoin dosage 2, 8 and 32 mg/kg/d) produced evidence of partial hair loss and elevated plasma triglycerides in the higher dose groups. The side effect spectrum of isotretinoin in the rodent thus closely resembles that of vitamin A, but does not include the massive tissue and organ calcifications observed with vitamin A in the rat. The liver cell changes observed with vitamin A did not occur with isotretinoin.

All observed side effects of hypervitaminosis A syndrome were spontaneously reversible after withdrawal of isotretinoin. Even experimental animals in a poor general state had largely recovered within 1–2 weeks.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

This medicine should not be used after the expiry date (EXP) shown on the pack.

Duplex blisters

Store in the original package and keep blister in the outer carton in order to protect from moisture and light.

Aluminium blisters
Store in the original package in order to protect from moisture and light.

4.2 Special Instructions for Use, Handling and Disposal

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems” if available in your location.

Return any unused Roaccutane capsules to the pharmacist.

Medicine: keep out of reach and sight of children.

4.3 Packs

Capsules 10 mg	30, 100
Capsules 20 mg	30, 100

Medicine: keep out of reach of children

Revision date: January 2020
Version: MYRoaccutane20200116CDS6.0

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland
by Catalent Germany Eberbach GmbH, Eberbach, Germany