Roaccutane is teratogenic. It should not be taken by pregnant women, women intending to become pregnant, or sexually active women in their fertile years, not using at least two methods of contraception, as severe malformations may occur during pregnancy.

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

Roaccutane® 10 mg capsules

Roaccutane® 20 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Roaccutane capsule contains 10 mg or 20 mg isotretinoin

Excipients with known effect:

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

Contains sugar (mannitol and sorbitol).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft gelatin capsules

Roaccutane 10 mg: Oval- brown-red, opaque capsules; imprint - ROA 10.

Roaccutane 20 mg: Oval - one half (along length) brown-red, opaque and the other half (along length) white, opaque capsules; imprint - ROA 20.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Severe recalcitrant nodular acne: Roaccutane is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflamed lesions with a diameter of 5 mm or greater. The nodules may become suppurative or haemorrhagic. “Severe”, by definition, means “many” as opposed to “few or several” nodules.

Because of significant adverse effects associated with its use, Roaccutane should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics.

A single course of therapy has been shown to result in complete and prolonged remission of disease in many patients. If a second course of therapy is needed, it should not be initiated until at least 8 weeks after completion of the first course, because experience has shown that patients may continue to improve while off Roaccutane.

4.2 Posology and method of administration

The initial diagnosis and prescription of Roaccutane should be performed by a dermatologist with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.

The therapeutic response to Roaccutane and its adverse events are dose-related, and vary between patients. This necessitates individual dosage adjustment during therapy.

Posology

Standard dosage

Therapy should be started at a dose of 0,5 mg/kg daily. For most patients the dose ranges from 0,5 - 1,0 mg/kg per day. Patients with very severe disease, or with truncal acne may require higher daily doses up to 2,0 mg/kg. A cumulative treatment dose of 120 - 150 mg/kg 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 a severe intolerance to

the recommended dose, treatment may be continued at a lower dose, with consequent increase in therapy duration.

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

Method of administration

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

Concurrent topical therapy

Concurrent administration of other keratolytic or exfoliative anti-acne agents is not indicated. Nor is concurrent radiation therapy with ultraviolet light indicated.

Patients should avoid exposure to the sun. Adjuvant therapy with mild topical medicines may be given, as required.

4.3 Contraindications

Pregnancy and lactation:

Roaccutane may not be given to breastfeeding mothers.

Roaccutane causes foetal malformations. These foetal malformations have been documented and include hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent external auditory canals), microphthalmia, cardiovascular abnormalities, facial dysmorphia, thymus gland abnormalities, parathyroid gland abnormalities with parathyroid hormone deficiency and cerebellar malformations. There is also an increased risk of spontaneous abortion.

Its use is therefore contraindicated, not only in women who are pregnant, or who may become pregnant while undergoing treatment, but also in all women of childbearing potential, unless an effective contraceptive is used, without any interruption, for one

month prior to therapy, the duration of therapy and for at least one month after discontinuation of therapy.

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 guidelines. It is recommended that two reliable forms of contraception be used simultaneously.

Roaccutane is contraindicated in women of child-bearing potential unless the female patient meets all the following conditions:

The patient must have severe nodular acne, resistant to standard therapies.

She must be reliable in understanding and carrying out instructions.

She must be informed by her doctor of the hazards of becoming pregnant during, and one month after, treatment with Roaccutane.

She must be warned of the possibility of contraception failure.

She must confirm that she has understood the precautions.

She must be capable of complying with the mandatory effective contraceptive measures.

She must use effective contraception, without any interruption, for 1 month before starting Roaccutane therapy, during therapy and for 1 month following discontinuation of therapy. Careful consideration must be given in each individual case to the efficacy of the contraceptive methods chosen, particularly in the first cycle of hormonal contraception when additional methods are advised.

She must have a negative result from a reliable pregnancy test within 11 days prior to the start of therapy. Monthly pregnancy testing during treatment is strongly recommended.

She must start Roaccutane therapy only on the 2nd or 3rd day of the next normal menstrual period.

In the event of relapse treatment, she must also use the same uninterrupted and effective contraceptive measures, 1 month prior to, during, and for 1 month after Roaccutane therapy, and the same reliable pregnancy evaluations should be followed.

She must fully understand the precautions and confirm her understanding and her willingness to comply with reliable contraceptive measures as explained to her.

Should pregnancy occur, in spite of these precautions, during treatment with Roaccutane, or during the first month after discontinuation, there is an extremely high risk of severe malformation of the foetus (involving in particular, the central nervous system, the heart and the large blood vessels), even after exposure for short periods only. Every possible precaution must be taken to ensure that the patient is not pregnant at the time of commencement of, during the course of, and for one month after discontinuation of therapy.

In order to assist prescribing physicians and patients in avoiding foetal exposure to isotretinoin, the manufacturer provides a Pregnancy Prevention Programme consisting of the following material to reinforce the warnings about the medicine's teratogenicity and emphasise the mandatory need for reliable contraception in female patients of childbearing potential:

Patient Information Brochure

Brochure on Birth Control

Female Patient Information and Consent Form

Physician's Guide to Prescription

Physician's Checklist for Prescription to Females

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

The Patient Information Brochure must be provided to *all* patients. In addition, all female patients must receive the Brochure on Birth Control and the Female Patient Information and Consent Form.

Roaccutane is also contraindicated in:

- Hypersensitivity to Roaccutane or any of its components. Roaccutane contains soya oil, partially hydrogenated soya oil, and hydrogenated soya oil. Therefore Roaccutane is contraindicated in patients allergic to soya.
- Pre-existing hypervitaminosis A.
- hepatic insufficiency.
- Patients with excessively elevated blood lipid values.
- Supplementary treatment with tetracyclines is contraindicated, (see section 4.5).

4.4 Special warnings and precautions for use

You are reminded that Roaccutane is a scheduled medicine and not a cosmetic agent and that it is a criminal act to transfer it to, or share it with, any person not in possession of a valid prescription.

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 Information Brochure.

Hepatotoxicity

Several cases of clinical hepatitis have been noted which are considered to be possibly or probably related to Roaccutane therapy. Liver function should be checked before and 1 month after the start of treatment, and subsequently, at 3 month intervals. Transitory 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, and do not return to normal values during treatment or if hepatitis is suspected, reduction of the dose or discontinuation of treatment should be considered.

Psychiatric disorders

Depression, aggravated depression, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and rarely, suicidal ideation, suicide attempts and suicide have been

reported in patients treated with Roaccutane (see section 4.8). 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. However, discontinuation of Roaccutane may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Pseudotumor cerebri

Cases of benign intracranial hypertension (pseudotumor cerebri) have been reported, some of which involved concomitant use of tetracyclines. (See section 4.5). Early signs and symptoms of pseudotumor cerebri include papilloedema, headache, nausea and vomiting and visual disturbances. Patients with these symptoms should be screened for papilloedema and, if present, they should be told to discontinue Roaccutane therapy immediately and be referred to a neurologist for further diagnosis and care. Supplementary treatment with tetracyclines is contraindicated, (see section 4.3).

Visual impairment

Corneal Opacities: Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. Due to the possible occurrence of keratitis, patients with dry eyes should be monitored.

Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.

Patients experiencing visual difficulties should be referred for an expert ophthalmological examination and withdrawal of Roaccutane considered.

Decreased night vision: Decreased night vision may occur during Roaccutane therapy, and may persist after discontinuation of therapy, (see section 4.8). 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.

Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion. Withdrawal of Roaccutane may be necessary.

Lipids

Serum lipids (fasting values) should also be checked, before, and one month after, the start of therapy, and also at the end of treatment. 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.

Approximately 25 % of patients receiving Roaccutane experience an elevation in plasma triglycerides. Approximately 15 % developed a decrease in high-density lipoproteins and about 7 % showed an increase in cholesterol levels. These effects on triglycerides, HDL and cholesterol were reversible upon cessation of Roaccutane therapy.

Roaccutane should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur. Levels in excess of 800 mg/dL or 9 mmol/L are sometimes associated with acute pancreatitis, which may be fatal (see section 4.8).

Special patient groups: 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 diabetic patients, frequent determination of blood glucose levels is recommended. New cases of diabetes mellitus have been diagnosed during Roaccutane therapy.

Musculo-skeletal and connective tissue disorders

Myalgia, arthralgia and increased serum creatine phosphokinase values have been reported in patients receiving Roaccutane, particularly in those undertaking vigorous physical activity.

Hyperostosis: In clinical trials for disorders of keratinisation with a mean dose of 2,24 mg/kg/day, a high prevalence of skeletal hyperostosis was noted. Additionally, skeletal hyperostosis was noted in 6 of 8 patients in a prospective study of disorders of keratinisation. Skeletal hyperostosis has also been observed by X-rays in prospective studies of nodular acne patients treated with a single course of therapy at recommended doses.

Premature epiphyseal closure: Bone changes including premature epiphyseal closure and calcification of tendons and ligaments have occurred after several years of administration at very 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.

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 (haemorrhagic) diarrhoea should discontinue Roaccutane immediately.

Pregnancy and lactation

Roaccutane IS TERATOGENIC.

Females of childbearing potential, as well as female patients who normally do not employ contraception because of a history of infertility, should be instructed that they must not be pregnant when Roaccutane therapy is initiated, and that they should use effective contraception while taking Roaccutane without any interruptions for 1 month prior to therapy, the duration of therapy and for 1 month after discontinuation of therapy. It is recommended that two reliable forms of contraception be used simultaneously. Micro-dosed progesterone preparation (mini-pills) may be an inadequate method of contraception during Roaccutane therapy. Although other hormonal contraceptives are effective, there have been reports of pregnancy from women who have used oral contraceptives, as well as injectable/implantable contraceptive medicines. These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with Roaccutane. Therefore it is important that women of childbearing potential use two effective forms of contraception simultaneously. They should also sign a Consent Form prior to beginning Roaccutane therapy (see boxed section 4.3).

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

- She has severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.
- She understands the teratogenic risk.
- She understands the need for rigorous follow-up, on a monthly basis.
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the duration of treatment and 1 month after the end of treatment. At least one and preferably two complementary forms of contraception including a barrier method should be used.
- Even if she has amenorrhoea she must follow all of the advice on effective contraception.
- She should be capable of complying with effective contraceptive measures.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.
- She understands the need and accepts to undergo pregnancy testing before, during and 5 weeks after the end of treatment.
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of isotretinoin.

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.

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 has used at least one and preferably two methods of effective contraception including a barrier method 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 5 weeks after the end of treatment. The dates and results of pregnancy tests should be documented.

Pregnancy testing:

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL are recommended to be performed in the first 3 days of the menstrual cycle, as follows.

Prior to starting therapy:

In order to exclude the possibility of pregnancy prior to starting contraception, it is recommended that an initial medically supervised pregnancy test should be performed and its date and result recorded. In patients without regular menses, the timing of this pregnancy test should reflect the sexual activity of the patient and should be undertaken approximately 3 weeks after the patient last had unprotected sexual intercourse. The prescriber should educate the patient about contraception.

A medically supervised pregnancy test should also be performed during the consultation when isotretinoin is prescribed or in the 3 days prior to the visit to the prescriber, and should have been delayed until the patient had been using effective contraception for at least 1 month. 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 28 day intervals. The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient's sexual activity and recent menstrual history (abnormal menses, missed periods or amenorrhoea). Where indicated, 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:

Five weeks after stopping treatment, women should undergo a final pregnancy test to exclude pregnancy.

Prescribing and dispensing restrictions:

Prescriptions of Roaccutane for women of childbearing potential should be limited to 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. Dispensing of Roaccutane should occur within a maximum of 7 days of the prescription.

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 medicine with anyone, particularly not females.

Additional precautions

Patients should be instructed never to give Roaccutane 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 foetus of a pregnant transfusion recipient.

Educational material

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 doctor to all patients, both male and female.

Skin and subcutaneous tissues 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 for a period of 5 - 6 months after the end of the treatment because of the risk of hypertrophic scarring in atypical areas and more rarely post inflammatory hyper or hypopigmentation in treated areas. Wax depilation should be avoided in patients on Roaccutane for at least a period of 6 months after treatment because of the risk of epidermal stripping.

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, Stevens-Johnson syndrome, and toxic epidermal necrolysis) associated with Roaccutane use. These events may be serious and result in death, life threatening events, hospitalisation, or disability. Patients should be monitored closely for severe skin reactions and Roaccutane should be discontinued if these occur

Renal insufficiency

Renal insufficiency and renal failure do not affect the pharmacokinetics of Roaccutane. 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.

Allergic reactions

Anaphylactic reactions have been reported, in some cases 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.

Sorbitol/mannitol intolerance

Roaccutane contains sorbitol and mannitol and may have a laxative effect.

Patients with the rare hereditary condition of sorbitol/mannitol intolerance should not take Roaccutane.

High Risk Patients

In patients with diabetes, obesity, alcoholism or a lipid metabolism disorder undergoing treatment with Roaccutane, more frequent checks of serum values for lipids and/or blood glucose may be necessary. Elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during Roaccutane therapy.

4.5 Interaction with other medicines and other forms of interaction

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

Cases of benign intracranial hypertension (pseudotumor cerebri) have been reported, some of which involved concomitant use of tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided. (See section 4.3).

No interactions between Roaccutane and other medicines have been observed to date.

4.6 Fertility, pregnancy and lactation

Pregnancy is an absolute contraindication to treatment with Roaccutane. If pregnancy does occur in spite of the detailed precautions during treatment with Roaccutane or in the month following therapy, there is a great risk of very severe and serious malformation of the foetus. (See section 4.3).

4.7 Effects on ability to drive and use machines

A number of cases of decreased night vision have occurred during Roaccutane therapy and in rare instances have persisted after 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 machines.

4.8 Undesirable effects

a. Summary of the safety profile

Every patient should be warned about the possible occurrence of side effects.

Most of the side effects of Roaccutane are dose-related.

b. Tabulated list of adverse reactions

Infections	
Very Rare (≤ 1/10 000)	Gram positive (mucocutaneous) bacterial infection
Blood and lymphatic system disorders:	
Very common (≥ 1/10)	Anaemia, increased red blood cell sedimentation rate, thrombocytopenia, thrombocytosis
Common (≥ 1/100, < 1/10)	Neutropenia
Very Rare (≤ 1/10 000)	Lymphadenopathy
Immune system disorders:	
Rare (≥ 1/10 000, < 1/1 000)	Allergic skin reaction, anaphylactic reactions, hypersensitivity
Metabolism and nutrition disorders:	
Very Rare (≤ 1/10 000)	Diabetes mellitus, hyperuricaemia
Psychiatric disorders:	
Rare (≥ 1/10 000, < 1/1 000)	Depression, aggravated depression, aggressive tendencies, anxiety, mood alterations
Very Rare (≤ 1/10 000)	Abnormal behaviour, psychotic disorder, suicidal ideation, suicide attempt, suicide
Nervous system disorders:	
Common (≥ 1/100,< 1/10)	Headache
Very Rare (≤ 1/10 000)	Benign intracranial hypertension, convulsions, drowsiness

Eye disorders:	
Very common (≥ 1/10)	Blepharitis, conjunctivitis, dry eye, eye irritation
Very Rare (≤ 1/10 000)	Blurred vision, cataract, colour blindness (colour vision deficiencies), contact lens intolerance, corneal opacity, decreased night vision, keratitis, papilloedema (as sign of benign intracranial hypertension), photophobia
Ear and labyrinth disorders:	
Very Rare (≤ 1/10 000)	Impaired hearing
Vascular disorders:	
Very Rare (≤ 1/10 000)	Vasculitis (e.g. Wegener's (eosinophilic) granulomatosis, allergic vasculitis)
Respiratory, thoracic and mediastinal disorders:	
Common (≥1/100, < 1/10)	Epistaxis, nasal dryness, nasopharyngitis
Very Rare (≤ 1/10 000)	Bronchospasm (particularly in patients with asthma), hoarseness
Gastrointestinal disorders:	
Very Rare (≤ 1/10 000)	Colitis, ileitis, dry throat, gastrointestinal haemorrhage, haemorrhagic diarrhoea and inflammatory bowel disease, nausea, pancreatitis (see section 4.4: *Gastrointestinal disorders*)
Hepatobiliary disorders:	
Very common (≥ 1/10)	Increased transaminase (see section 4.4: *Lipids*)
Very Rare (≤ 1/10 000)	Hepatitis
Skin and subcutaneous tissues disorders:	
Very common (≥ 1/10)	Cheilitis, dermatitis, dry skin, localised exfoliation,

	pruritus, erythematous rash, skin fragility (risk of frictional trauma)
Rare (≥ 1/10 000, <1/1 000)	Alopecia
Very Rare (≤ 1/10 000)	Acne fulminans, aggravated acne (acne flare), erythema (facial), exanthema, hair disorders, hirsutism, nail dystrophy, paronychia, photosensitivity reaction, pyogenic granuloma, skin hyperpigmentation, increased sweating
Musculo-skeletal and connective tissue disorders:	
Very common (≥ 1/10)	Arthralgia, myalgia, back pain (particularly adolescent patients)
Very Rare (≤ 1/10 000)	Arthritis, calcinosis (calcification of ligaments and tendons), epiphyses premature fusion, exostosis, (hyperostotis), reduced bone density, tendonitis
Renal and urinary disorders:	
Very Rare (≤ 1/10 000)	Glomerulonephritis
General disorders and administration site conditions:	
Very Rare (≤ 1/10 000)	Increased formation of granulation tissue, malaise
Investigations:	
Very common (≥ 1/10)	Increased blood triglicerides, decreased high density lipoprotein
Common (≥1/100, < 1/10)	Increased blood cholesterol, increased blood glucose, haematuria, proteinuria
Very Rare (≤ 1/10 000)	Increased blood creatine phosphokinase

The incidence of the adverse events was calculated from pooled clinical trial data involving 824 patients.

Post Marketing

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

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

4.9 Overdose

Although the acute toxicity of Roaccutane is low, signs of hypervitaminosis A could appear in cases of accidental overdose. Evacuation of the stomach may be indicated in the first few hours after overdose. Further treatment is supportive and symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Isotretinoin, the active ingredient of Roaccutane, is a synthetic stereoisomer of all-trans retinoic acid (tretinoin). The mechanism of action of isotretinoin has not been elucidated, but the action is associated with dose-related 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.

5.2 Pharmacokinetic properties

Time-related blood concentrations can be predicted from single-dose data on the basis of linear pharmacokinetics. This property also provides some evidence that the activity of hepatic drug metabolising enzymes is not induced by isotretinoin.

Absorption:

Oral absorption of isotretinoin is optimal when taken with food or milk. After oral administration of 80 mg, peak blood concentrations ranged from 167 ng/mL to 459 ng/mL (mean 256 ng/mL) and were achieved in 1 - 6 hours (mean 3,2 hours) in healthy volunteers, while in acne patients

peak concentrations ranged from 98 ng/mL to 535 ng/mL (mean 262 ng/mL), and occurred at 2 to 4 hours after administration (mean 2,9 hours). The mean ± Standard Deviation (SD) minimum steady-state blood concentration of isotretinoin was 160 ± 19 ng/mL. The terminal elimination half-life was consistent with that observed in healthy subjects.

Distribution:

Isotretinoin is 99,9 % bound to plasma proteins, primarily albumin. Steady state blood concentrations ($C_{min.ss}$) of isotretinoin in patients with severe acne treated with 40 mg two times a day ranged from 120 - 200 ng/mL; the concentration of 4-oxo-isotretinoin in these patients were 2 - 5 times higher than the isotretinoin concentrations.

Metabolism:

After oral administration of isotretinoin, three 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.

Isotretinoin metabolites have shown biological activity in several *in-vitro* tests. Thus the observed clinical profile in patients could be the result of the pharmacological activity of isotretinoin and its metabolites. 4-oxo-isotretinoin is a significant contributor to the activity of Roaccutane.

Since isotretinoin and tretinoin (all-trans retinoic acid) are reversibly metabolised (= interconverted), the metabolism of tretinoin is 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.

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.

Elimination:

After oral administration of radiolabeled isotretinoin, approximately equal fractions of the dose were recovered in urine and faeces. The terminal elimination half-life of unchanged medicine 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.

Pharmacokinetics in special populations:

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients:

Capsule filling:

Beeswax yellow, soya-bean oil.

Capsule shell:

Gelatin, glycerol, karion 83 (consisting of sorbitol, mannitol, hydrogenated hydrolysed starch), titanium dioxide (E171), red iron oxide (E172).

Printing ink:

Black iron oxide (E172), modified shellac, propylene glycol.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store aluminium and triplex blisters at or below 30 °C and protect from light.

Store duplex blisters at or below 25 °C and protect from light.

Do not use after expiry date shown on the pack.

Store all medicines out of reach of children.

Any unused product or waste material should be disposed of.

6.5 Nature and contents of container

Roaccutane 10 mg capsules: available in blister packs containing 30 or 60 capsules.

Roaccutane 20 mg capsules: available in blister packs containing 30 or 60 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene, Pretoria

South Africa

0157

8. REGISTRATION NUMBER(S)

Roaccutane 10 mg: R/13.4.2/118

Roaccutane 20 mg: R/13.4.2/119

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Registration: 18 September 1984

10. DATE OF REVISION OF THE TEXT

Last revision: 12 August 2022

Roaccutane 20 mg Capsules
Botswana: S2 B9310510
Namibia: S3 90/13.4.2/001424

Approved Manufacturer:

Catalent Germany Eberbach GmbH

Gammelsbacherstrasse 2

69412 Eberbach

Germany