

Isotretinoin

Category

1. DESCRIPTION**1.1 Therapeutic / Pharmacologic Class of Drug**

Retinoid for systemic treatment of acne

ATC Code: D10BA01

1.2 Type of Dosage FormCapsules: *soft*: 10 mg and 20 mg**1.3 Route of Administration**

Oral

1.4 Qualitative and Quantitative CompositionActive 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 hydrolyzed starch; Titanium dioxide (E171); Red iron oxide (E172).

Dry printing ink:

Shellac, modified; Black iron oxide (E172); Propylene glycol.

Capsules 10 mg

Capsules 20 mg

2. CLINICAL PARTICULARS**2.1 Therapeutic Indication(s)**

Roaccutane is indicated for the treatment of severe forms of acne (nodulo-cystic forms) and acne, which has failed to respond to other therapies.

Roaccutane should only be prescribed by physicians who are experienced in the use of systemic retinoids- preferably dermatologists- and understand the risk of teratogenicity if Roaccutane is used during pregnancy.

2.2 Dosage and Administration

Standard dosage

The therapeutic response to Roaccutane and its adverse events are dose-related and varies 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 0.5-1.0 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 dose of 120 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.

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

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) and afterwards individually adjusted according to tolerance.

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 who may become pregnant while undergoing treatment 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

- Patients 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**Roaccutane is highly **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 childbearing 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**The female patient must ensure that:**

- She understands the teratogenic risk.
- She is reliable in understanding and carrying out instructions.
- She must be informed by her physician of the hazards of becoming pregnant during and 1 month after treatment with Roaccutane.
- She understands and accepts the need for effective contraception without any interruption for 1 month before beginning Roaccutane therapy, during therapy and for 1 month following discontinuation of therapy. At least one highly effective method of contraception (i.e. a user-independent form), or two complementary user-dependent forms of contraception including a barrier method must be used.
- She must have a negative result from a medically supervised pregnancy test within 11 days prior to the start of therapy. She must accept to undergo pregnancy testing during treatment and 5 weeks after the end of treatment.
- She must start Roaccutane therapy only on the 2nd or 3rd day of the next normal menstrual period.
- She must be warned of the possibility of contraception failure.
- She understands the need for rigorous follow-up on a monthly basis.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.
- Even if she has amenorrhoea she must follow all of the advice on effective contraception.
- 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 willingness to comply with reliable contraceptive measures as explained to her.
- She must be capable of complying with the mandatory effective contraceptive measures. 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 potential for pregnancy has been assessed for all female patients.
 - The patient must have 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.
 - 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 form) or two complementary user-dependent forms of 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.
 - 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.
- Should pregnancy occur in spite of these precautions during treatment with Roaccutane or in the month following, there is a great risk of very severe malformation of the foetus (involving in particular the central nervous system, the heart and the large blood vessels). There is also an increased risk of spontaneous abortion. If pregnancy does occur, the physician and patient should discuss the advisability of continuing the pregnancy.

Contraception

- o 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.
- o As 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, including a barrier method. Contraception must be continued for at least 1 month after stopping treatment with Roaccutane, even in patients with amenorrhoea.

Pregnancy testing

- o According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25mIU/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 Roaccutane 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 amenorrhea). 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.

Educational material

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

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

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.

Male patients:

The available data suggest that the level of maternal exposure from the semen and seminal fluid 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 not 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 for disposal.

Donation of blood by patients should be avoided during and within 1 month after cessation of Roaccutane treatment to prevent an accidental exposure and the potential risk to the foetus of a pregnant transfusion recipient.

Psychiatric disorders

Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms and very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with Roaccutane (see section 2.6 Undesirable Effects). 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. Awareness by family or friends may be useful to detect mental health deterioration.

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 hypopigmentation 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-moisturizing 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, hospitalization, 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). Isolated instances of raised serum CPK values have been reported in patients receiving Roaccutane, particularly those undertaking vigorous physical activity.

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 keratinization. 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 and administration restricted to severe cases of acne.

Benign intracranial hypertension

Rare cases of benign intracranial hypertension "pseudotumor cerebri" have been reported, some of which involved concomitant use of tetracyclines (see section 2.4.5 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, before and 1 month after the start of therapy, and subsequently at 3 months interval 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 Drug Abuse and Dependence

Not applicable.

2.4.3 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 foetus.

See section 2.3 Contraindications.

Risks to the Developing Embryo/Foetus

The foetal malformations associated with exposure to Roaccutane include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial dysmorphism, 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.

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. Roaccutane may affect long bone growth in children who are still growing. The use of Roaccutane for the treatment of severe recalcitrant nodular acne in pediatric patients age 12 to 17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists. Clinical study has shown that Roaccutane, at a dose of 1mg/kg/day given in two divided doses, was effective in treating recalcitrant nodular acne in patients age 13 to 17 years.

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 tendon and other bone changes, reduced bone density, back pain, epiphyses, premature fusion, tendinitis.

Psychiatric and central nervous system disorders

Behavioral 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.

Rare (may affect up to 1 in 1,000 people):

Depression, depression aggravated, aggressive tendencies, anxiety, mood alterations.

Very rare (may affect up to 1 in 10,000 people):

Suicide, suicide attempt, suicidal ideation, psychotic disorder, abnormal behavior.

Sensory disorders

Isolated cases of visual disturbances, photophobia, dark-adaptation disturbances (decreased night vision), rarely color 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 Postmarketing 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 hospitalization and some with fatal outcome, have been reported, particularly in those undertaking vigorous physical activity. Sexual dysfunction including erectile dysfunction and decreased libido have also been reported.

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 synthetic 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 antiinflammatory 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 program 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 ($\geq 99.9\%$); 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 120-200 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-vitro tests. 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 isomerization.

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. CYP2C8, CYP2C9, CYP2B6, and possibly CYP3A4 appear to have the greatest contributions in the metabolism of isotretinoin to 4-oxo-isotretinoin. CYP2C9, CYP2B6, and possibly CYP2C8, CYP3A4, CYP2A6, and CYP2E1 contribute to the metabolism of isotretinoin. CYP 26 is also known to metabolize retinoids.

Roaccutane and its metabolites do not significantly affect CYP activity.

3.2.4 Elimination

After oral administration of radiolabeled 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

Duplex blisters

Store in the original package and keep blister in the outer carton in order to protect from moisture and light. Do not store above 30°C.

Aluminium blisters

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

Shelf life:

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

4.2 Special Instructions for Use, Handling and Disposal

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Return any unused Roaccutane capsules to the pharmacist.

4.3 Packs

Capsules 10 mg	30
Capsules 20 mg	30

Medicine: keep out of reach and sight of children

Current at August 2019



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