Composition
Active ingredient: isotretinoin (1 13-cis-retinoic acid)
10 mg and 20 mg capsules.
Excipients: coloring agents (E161, E171).

Properties
Isotretinoin, the active ingredient of Roaccutane, is a synthetic stereoisomer of all-trans-retinoic acid (tretinoin).
The mechanism of action of Roaccutane has not yet been fully elucidated. However, it is clear that the clinical improvement seen in severe acne is paralleled by a dose-dependent reduction in the activity of the sebaceous glands and a histologically confirmed decrease in their size. Isotretinoin has also been shown to have an anti-inflammatory effect in the skin.

Pharmacokinetics
Time-dependent blood concentration profiles can be predicted on the basis of linear pharmacokinetics.

Absorption
Peak plasma concentrations (Cmax) of approximately 250 ng/ml were measured one to four hours (tmax) after isotretinoin 80-100 mg in healthy volunteers and patients with cystic acne.
Taking isotretinoin together with food increases its bioavailability to as much as twice the value in the fasting state, very probably due to facilitated absorption of this highly lipophilic drug. In general, there is also less variation in systemic availability if isotretinoin is taken with meals.

Distribution
Isotretinoin displays very high plasma protein binding (>99.9%), so that the unbound fraction of the drug is less than 0.1% over a wide range of therapeutic concentrations. Albumin appears to be the preferred binding protein.
The volume of distribution of isotretinoin in man is unknown, as no intravenous dosage form exists. Isotretinoin crosses the placental barrier in amounts sufficient to cause fetal malformations. Because of its lipophilic character, it is highly likely that isotretinoin is secreted in human milk. Isotretinoin is therefore contraindicated in nursing mothers.

Metabolism
The principal metabolite of isotretinoin in the blood is 4-oxo-isotretinoin, which is rapidly formed after oral administration of the product. Isotretinoin also isomerizes in vivo to tretinoin (all-trans-retinoic acid), which represents an alternative metabolic pathway. Although formation of glucuronides from the metabolites has not been conclusively demonstrated in humans, strong evidence for this has been provided by animal studies. Data collected in humans and dogs suggest that isotretinoin undergoes enterohepatic recirculation, which would contribute to the interindividual variations in plasma concentration.

Elimination
Isotretinoin appears to be eliminated almost exclusively by metabolism in the liver and excretion in the bile. After oral administration to healthy volunteers and patients with cystic acne, the elimination half-life of unaltered isotretinoin ranged from 7 to 39 hours (mean: approximately 20 hours).
The mean elimination half-life of the 4-oxo-metabolite in patients with cystic acne was slightly higher (25 hours; range 17-50 hours) than that of the parent substance.

Kinetics in Special Situations
Since isotretinoin is contraindicated in renal or hepatic impairment, no data are available on the pharmacokinetics of the drug in these patients.

Indications
Severe forms of acne, especially nodulocystic acne and forms of acne with a tendency to scarring. Roaccutane should only be prescribed by doctors who are experienced with the use of systemic retinoids (preferably dermatologists) and clearly under-
stand the risk of malformations if Roaccutane is taken during pregnancy.

Contraindications
Roaccutane is contraindicated in pregnancy (see below), renal or hepatic impairment, hypervitaminosis A, severe hyperlipidemia, hypersensitivity to the product and in combination with tetracyclines.

Side Effects
Most side effects of Roaccutane are dosedependent. At the recommended doses the extent of side effects is generally acceptable to the patient, given the severity of the condition being treated. The commonest side effects are symptoms resembling those of hypervitaminosis A, notably dryness of mucous membranes, which on the lips can be relieved by applying a greasy ointment. Dryness of the nasal mucosa and throat may lead to epistaxis and hoarseness. Additional side effects observed especially at high dosage are listed under organ systems below.

Skin and Appendages
Acne may worsen temporarily at the start of treatment with Roaccutane. However, this gives way to progressive improvement as treatment is continued. Rashes, pruritus, facial dermatitis, facial hyperpigmentation, pyogenic granulomas, increased production of granulation tissue in acne lesions, local or systemic infections with Gram-positive microorganisms (Staphylococcus aureus), and paronychia and nail dystrophy have occasionally been observed. Reversible hair loss is occasionally seen, as well as rare cases of irreversibly thin hair or hirsutism. Increased sensitivity to sunburn may occur in rare cases.

There have been sporadic reports of acne fulminans and lymphadenopathy, although these do not appear to be causally related to the treatment.

Eyes
Dryness of the eyes, which may persist for up to a year or more after stopping Roaccutane, often leads to conjunctivitis and reversible corneal clouding. The conjunctivitis is improved by a mild eye ointment. Contact lens wearers may be forced by ocular irritation to wear glasses for the duration of treatment. Isolated cases of impaired dark adaptation (decreased night vision) and cataracts have been reported. There have been sporadic reports of visual disturbances.

Keratitis has been observed in rare cases during treatment with Roaccutane and may be related to dry eye syndrome. Patients—especially those with dry eye syndrome—should therefore be monitored for the development of keratitis.

Musculoskeletal System
Muscle and joint pain have been observed in rare cases. Bone changes and hyperostoses have occurred in children (e.g. premature epiphyseal fusion) and adults during long-term treatment with high Roaccutane doses for other indications. One patient treated for many years with etretinate, another retinoid, developed spinal hyperostoses and calcification of spinal ligaments, which led to spinal cord compression. Although Roaccutane is not intended for long-term use, attention must be drawn to the possibility of these Side Effects if the product is nevertheless used inappropriately in this way. Minimal hyperostoses have occasionally been observed after the end of conventional treatment for cystic acne. Because of the possibility of such bone changes, the potential benefits and risks must be carefully weighed in every patient, and Roaccutane used only in severe cases.

Central Nervous System
There have been rare reports of nausea, headache, sweating and hearing impairment in certain frequency ranges. CNS disturbances, such as convulsions, have occasionally been observed. There have been sporadic reports of benign intracranial hypertension. Roaccutane has been implicated in cases of depression, which in some cases resolved on stopping treatment and returned on recommencement. The possibility of suicide must be borne in mind (see Precautions). Behavioral disturbances and psychotic states have also been reported.
Every patient must be informed of the possibility of side effects.

Precautions
Liver function tests should be performed before and one month after the start of treatment, then again after 3 months.

Fasting serum lipid levels should also be monitored (before and two weeks after the start of treatment, and at the end of the 3- to 4-month treatment period). More frequent monitoring may be required if Roaccutane is used in high-risk patients (diabetes, obesity, alcoholism, disturbances of lipid metabolism). Blood glucose levels should be checked more frequently in known or suspected diabetes. Although an association with Roaccutane has not been confirmed, raised fasting blood glucose and new cases of diabetes have been reported during treatment with Roaccutane.

Rare cases of benign intracranial hypertension have been reported following treatment with Roaccutane, a phenomenon also observed with tetracyclines. Concomitant treatment with tetracyclines is therefore contraindicated.

Roaccutane has been linked to adverse psychological effects, especially depressive states. Prescribers must be alert to such symptoms and take seriously the potential risk of suicide. Once Roaccutane has been discontinued, additional diagnostic and therapeutic measures should be considered.

Patients must not donate blood during treatment with Roaccutane and for up to two weeks after treatment has ended.

Pregnancy
Roaccutane is teratogenic. Its use is therefore contraindicated not only during pregnancy but also in women who could become pregnant during treatment. There is an extremely high risk of fetal malformation if Roaccutane is taken during pregnancy, even for only a short time.

Women of child-bearing age may be treated with Roaccutane only if all of the following conditions are met:

Gastrointestinal Tract
Intestinal upsets, including colitis, ileitis and hemorrhage, have been observed in rare cases.

Hepatic Effects
Transient, reversible increases in transaminase levels are frequently observed. Although such changes often remain within the normal range and resolve during continued treatment, there have also been cases that necessitated dose reduction or discontinuation of Roaccutane. If transaminases rise to twice the normal upper limit or above, the dose must be reduced and thought given to the advisability of further treatment. If pathological liver function indices persist after dose reduction, treatment should be stopped. There have been occasional cases of hepatitis possibly related to the product.

Serum Lipids
Raised serum triglyceride and cholesterol levels and reduced HDL have often been observed, especially at high doses and in predisposed individuals (history of disordered lipid metabolism, diabetes, obesity or alcoholism). These changes too are dose-dependent and resolve rapidly after reducing the dose or discontinuing treatment. If serum triglyceride or cholesterol levels rise to twice the normal upper limit or above, the dose must be reduced and thought given to the advisability of further treatment. If pathological values persist after dose reduction, treatment should be stopped.

Patients with high serum triglyceride levels (>800 mg/dl) are at risk of developing pancreatitis during treatment with isotretinoin.

Miscellaneous
Changes in the red or white blood cell count (e.g. anemia or neutropenia), increased and decreased platelet counts, and raised erythrocyte sedimentation rates have been observed in rare cases. Vasculitis (e.g. Wegener’s granulomatosis), hyperuricemia, hematuria/proteinuria, gynecomastia and hyperprolactinemia have occasionally been reported. There have been isolated cases of bronchospasm, and caution should be exercised in pre-disposed individuals.
1. Treatment with Roaccutane must be clearly indicated.
2. The patient has been informed by her doctor of the dangers of becoming pregnant during treatment with Roaccutane and for one month afterwards. She has also been warned about the possibility of contraceptive failure.
3. It is certain that she understands and will follow her doctor’s orders, and confirms this to her doctor.
4. She is willing and able to use reliably the obligatory contraceptive measures.
5. A pregnancy test performed no more than two weeks before starting treatment must be negative. Further pregnancy tests must be performed every month during treatment,
6. The patient practices effective contraception uninterruptedly from one month before until one month after treatment with Roaccutane.
7. Treatment with Roaccutane is started only on the second or third day of the next normal menstrual cycle.
8. If treated for relapses, the patient practices the same effective contraception uninterruptedly from one month before until one month after treatment with Roaccutane.

Even women using no contraception because of preexisting infertility should be urged to follow the above guidelines for as long as they take Roaccutane.

If the patient nevertheless becomes pregnant during treatment with Roaccutane or in the month following treatment, there is a high risk of extremely severe fetal malformations (mainly involving the central nervous system, heart and major blood vessels). There is also an increased risk of spontaneous abortion.

The following extremely severe malformations have been reported in the children of mothers who have taken Roaccutane during pregnancy: hydrocephalus, microcephaly, deformity of the pinna of the ear (microtia), small or absent external auditory canal, microphthalmia, cardiovascular malformations, facial dysmorphism, abnormal thymus morphology, parathyroid hypofunction and cerebellar malformations.

Lactation
Roaccutane must not be administered to nursing mothers.

Overdosage
Although the acute toxicity of Roaccutane is low, accidental overdosage could produce symptoms of hypervitaminosis A. Although these are reversible, gastric lavage may be indicated in the first few hours.

Stability
The product must not be used after the date marked EXP on the container.

Drug Interactions
Roaccutane should not be administered concomitantly with vitamin A, as this could exacerbate symptoms of hypervitaminosis A. Since tetracyclines may likewise increase intracranial pressure, their combination with Roaccutane is contraindicated.

Additional interactions between Roaccutane and other drugs (such as oral contraceptives) have not been observed.

Dosage and Administration
Treatment should be started with 0.5 mg/kg body weight daily. A brief worsening of the acne at the start of treatment is not unusual. Since patients vary in their response to and toleration of the drug, the dose for the remainder of the treatment should be individually adjusted after about 4 weeks up to maximum of 1 mg/kg daily. The duration of treatment is calculated on the basis of the cumulative dose. Several studies have shown that the cumulative dose for a treatment cycle lasting several months should be between 100 and 150 mg/kg to prevent recurrence. If the condition nevertheless recurs, a further course of treatment can be prescribed. The capsules are taken once daily with meals.

Concurrent Topical Treatment
Concurrent use of other keratolytic or exfoliative antiacne drugs or UV phototherapy is not indicated. Sun exposure should be avoided.