Oratane* 5mg, 10 mg and 20 mg Capsules

Packaging Insert

Isotretinoin 5 mg, 10 mg and 20 mg Soft Gelatin Capsules

douglas

PRESENTATION

ORATANE 5 mg capsules are faint pinkish-cream to cream coloured, oval, soft-gelatin capsules containing a yellow/ orange, opaque, viscous liquid. ORATANE 10 mg capsules are opaque, violet, oval, length 10 mm and diameter 7 mm, containing 10 mg of isotretinoin.
ORATANE 20 mg capsules are opaque, maroon, oval, length 13 mm and diameter 8 mm, containing 20 mg of isotretinoin.

ACTIONS

Isotretinoin is a retinoid with a specific antiseborrheic action for oral treatment of severe cystic acne and conglobate acne resistant to other forms of treatment. Isotretinoin, the active ingredient of ORATANE, is a synthetic stereoisomer of alltrans retinoic acid (tretinoin), an active substance which has proved effective in topical treatment of acne vulgaris, Isotretinoin is chemically identified as 13-cis retinoic acid: (2Z, 4E, 6E, 8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl) nona-2,4,6,8-tetraenoic acid, molecular weight 300.42 and molecular formula is $C_{20}H_{28}O_2$ Administered orally, isotretinoin has a marked effect in severe forms of acne, which have proved insufficiently responsive to previous treatment. The mechanism of action of isotretinoin 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 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.

PHARMACOKINETICS

Time-related blood concentrations can be predicted on the basis of linear pharmacokinetics.

Absorption:

Peak plasma concentrations (Cmax) of approximately 200-300ng/ml have been achieved in healthy volunteers three to four hours (tmax) after administration of 40 mg isotretinoin. Taking isotretinoin with food increases bioavailability up to twofold relative to fasting conditions, probably as a result of easier absorption of this highly lipophilic medication. Furthermore, there is an overall decrease in fluctuations in systemic availability when isotretinoin is ingested with food.

Distribution:

Isotretinoin is extensively bound to plasma proteins (99.9%) with the result that the free active fraction of the substance is less than 0.1% of the total over a wide range of therapeutic concentrations. Albumin appears to be the major binding protein. The volume of distribution of isotretinoin is not known in humans since it is not available as an intravenous preparation.

Metabolism:

Three major metabolites have been identified in plasma: 4-oxo-isotretinoin, tretinoin (all-trans retinoic acid), and 4-oxo-tretinoin. The major blood metabolite of isotretinoin is 4-oxo-isotretinoin, which is rapidly formed following oral administration achieving peak concentrations of 100 - 140 ng/ml at about two hours after administration of 40 mg isotretinoin. Other minor metabolites have been detected but are not completely identified, which also includes glycuronides 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.
Isotretinoin also isomerises in vivo via an alternative metabolic pathway to tretinoin (all-trans retinoic acid). Glucuronidation of the metabolites has not been conclusively demonstrated in humans but is strongly suggested by animal studies.
Investigations in humans and dogs point to an enterohepatic recirculation of isotretinoin, which would contribute to the observed interindividual variability in plasma concentrations.
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.

Elimination:

Isotretinoin appears to be eliminated almost exclusively by hepatic metabolism and biliary excretion. Following oral administration of isotretinoin, the elimination half life of unchanged substance has ranged from 7 to 39 hours (mean approximately 20 hours) in both healthy volunteers and patients with cystic acne. The mean elimination half-life of the 4-oxo metabolite in patients with cystic acne is slightly longer (25 hours, range: 17-50 hours) than that of the parent substance, Isotretinoin is a physiological retinoid and endogenous retinoid concentrations are reached within approximately two weeks following the end of isotretinoin therapy. Since isotretinoin is contraindicated in patients with renal or hepatic impairment, there is no information on the pharmacokinetics of the substance in this population. In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 10 mg/day) and afterwards individually adjusted according to tolerability.

INDICATIONS

ORATANE 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.

ROUTE OF ADMINISTRATION

Oral administration

DOSAGE AND ADMINISTRATION

Isotretinoin 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 Warnings and Precautions and Use in Special Populations).

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

Special Dosage Instructions

Renal impairment
In patients with severe renal insufficiency, isotretinoin 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 Renal Impairment).

ADVERSE EFFECTS

Most of the adverse effects of isotretinoin are dose related. In the proper dosage, tolerability is generally acceptable in view of the severity of the disease. Every patient should be warned about the possible occurrence of adverse effects.

HYPERVITAMINOSIS A:

The most frequently observed symptoms are those associated with hypervitaminosis A, i.e. dryness of the mucosae, which on the lips can be relieved by the application of a fatty ointment, dryness of the nasal mucosa which can lead to epistaxis and dryness of the pharyngeal mucosa, hoarseness, and dryness of the vaginal and/or anal mucosa.

EYES:

Dryness of the eyes can cause conjunctivitis and reversible corneal opacities. Conjunctivitis can be improved by a mild eye ointment. Intolerance to contact lenses may force the patient to wear glasses during treatment. Isolated cases of photophobia, dark adaptation disturbances (decreased night vision) and lenticular cataracts have been reported. Keratitis in association with isotretinoin treatment is a rare event and possibly related to the dry eye syndrome. Therefore patients, particularly those with dry eye syndrome, should be monitored for the development of keratitis.

SKIN:

Exanthema, pruritus, dermatitis facialis, sweating, pyogenic granuloma, paronychia, nail dystrophy and increased formation of granulation tissue may occur. Rare cases of persistent hair thinning have been reported. Reversible alopecia has been observed. Hirsutism, acne fulminans and hyperpigmentation (facial) have been reported rarely. Rarely, patients may experience photosensitivity reactions.

BONE:

Bone changes and hyperostosis have occurred in children (including premature epiphyseal closure) and adults treated over long periods with high doses of isotretinoin generally for indications other than cystic acne. In one patient, spinal hyperostosis and clarification of the spinal ligaments with subsequent compression of the spinal cord were observed following long term treatment over several years with another retinoid, etretinate. Isotretinoin is not intended for long term therapeutic use, and the possibility of this adverse effect occurring if it is used improperly for long term treatment should be borne in mind. Minimal hyperostosis has been observed in cystic acne patients treated with a single course of isotretinoin. Due to the possible occurrence of these bone changes, a careful evaluation of this risk/benefit ratio should be carried out in every patient and isotretinoin administration should be restricted to severe cases.

HAEMATOLOGY:

There have been cases of allergic vasculitis including Wegener's granulomatosis, decreases in white and red blood cell counts including anaemia and neutropenia, increases and decreases in platelet count, elevated sedimentation rate.

RESPIRATORY SYSTEM DISORDERS:

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

PSYCHIATRIC AND CENTRAL NERVOUS SYSTEM DISORDERS:

Behavioural disorders, depression (see Precautions), headache, increased intracranial pressure (pseudotumorcerebri) and seizures.

LABORATORY DATA:

Transitory and reversible increases in transaminases as well as some cases of hepatitis related to isotretinoin have been observed. 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 dosage or discontinue treatment with isotretinoin. Increases in serum triglyceride and cholesterol levels as well as a decrease of HDL have also been observed, particularly at high dosages and in predisposed patients (with a family history of lipid metabolism disorders, diabetes, obesity or alcoholism). These changes too are dose-related, and values return to normal on reduction of the dosage or withdrawal of the medicine.

OTHER EFFECTS:

Isolated cases of benign intracranial hypertension and visual disturbances, and occasionally nausea and headache have or systemic infections due to Gram-positive microorganisms (Staphylococcus aureus) have been reported. Muscle and joint pain and, more rarely, overdosage, inflammatory bowel disease (eg. Colitis, ileitis haemorrhage), and hyperuricaemia have been reported. Lymphadenopathy has occasionally been noted.

CONTRAINDICATIONS

- Pregnant women
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (See Section Warnings & Precautions)

WARNINGS AND PRECAUTIONS

ORATANE is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects.

ORATANE is strictly contraindicated in:

- Pregnant women
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met

Pregnancy Prevention Programme

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

- [approved indication] (See Sections Indications)
- 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 user-independent form) or two complementary userdependent 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 advise 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 ORATANE. This condition also concerns 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

Description: Oratane CAPS PI MY 310100
Size: 510 x 210 mm
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The prescriber must ensure that:

- The patients complies with the conditions for pregnancy has an adequate level of understanding
- The patients 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 on highly effective method of contraception (i.e a user-independent form) or two complementary userdependent 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 test should be documented

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

If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the fetus. This 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 advise 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.

As a minimum requirement, female patients of childbearing 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 ORATANE, 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 start 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 ORATANE

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 potentials, the prescription duration of ORATANE 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 ORATANE should occur on the same day.

This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patients 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 ORATANE is not of a sufficient magnitude to be associated with the teratogenic effects of ORATANE. Male patients should be reminded that they must not share their medication with anyone, particularly females.

Additional precautions

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 ORATANE because of the potential risk to the foetus of a pregnant transfusion recipient.

Educational material

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

Prescribers should inform the individual patient of the risks associated with the use of isotretinoin. Isotretinoin should only be prescribed by doctors who are experienced in the use of systemic retinoids and understand the risk of teratogenicity associated with isotretinoin therapy.
Hypersensitivity reactions may occur in susceptible individuals.

Psychiatric Symptoms

Depression, depression aggravated, anxiety, and mood alterations 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.

Liver problems

Liver function should be checked before and one month after the start of treatment and subsequently at three-monthly intervals.
Serum lipids (fasting value) should also be checked (before and one month after the start of therapy, and also at the end of the three-to-four-month treatment period). In high risk patients (with diabetes, obesity, alcoholism or disturbances of the lipid metabolism) undergoing treatment with isotretinoin, more frequent checks may be necessary. Isotretinoin should not be used together with any medicine known to enhance liver metabolism or interfere with enterohepatic circulation.
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. In known or suspected diabetic patients, frequent determination of blood glucose levels is recommended. Although no causal relationship has been established, elevated fasting blood sugars have been reported and new cases of diabetes have been diagnosed during isotretinoin therapy.
It is recommended that clinically significant serum triglyceride elevations be controlled, since levels in excess of 800 mg/dL are sometimes associated with acute pancreatitis, which is known to be potentially fatal. Hence, isotretinoin should be discontinued if uncontrolled hypertriglyceridaemia or symptoms of pancreatitis occur.
Patients, particularly those with dry eyes, should be monitored for the development of keratitis.
Rare cases of benign intracranial hypertension have been reported after isotretinoin and after tetracyclines. Supplementary treatment with tetracyclines is, therefore, contraindicated.
Myalgia and arthralgia may occur and may be associated with reduced tolerance to vigorous exercise (see Adverse effects). Isolated instances of raised serum CPK values have been reported in patients receiving isotretinoin, particularly those undertaking vigorous physical activity.
Hyperostosis has been seen in some patients suffering from keratinising dermatoses on treatment with higher doses (> 2 mg/kg) and long-term administration (> 1 year). Blood donation to women of childbearing age by patients being treated or recently treated (one to two weeks) with isotretinoin is contraindicated.

Skin problems

Aggressive dermabrasion should be avoided in patients on isotretinoin and for a period of 5-6 months after treatment because of the risk of hypertrophic scarring in atypical areas. Wax epilation should be avoided during therapy and at least for a period of 6 months thereafter due to the possibility of scarring or dermatitis.

Gut and stomach problems

Isotretinoin 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 isotretinoin immediately

USE IN PREGNANCY

Pregnancy

Isotretinoin is highly teratogenic and must not be given to women who are pregnant. Isotretinoin crosses the placental barrier in amounts that lead to congenital deformities. There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking ORATANE in any amount even for short periods. Potentially all exposed foetuses can be affected.

Use in Lactation

Owing to its lipophilicity, there is a high probability that isotretinoin is secreted into the breast milk.

Use in Children

Long term use in children under 13 years should be avoided because of a risk of premature epiphyseal closure.

Effects on Ability to Drive or Operate Machinery

Decreased night vision has occurred during and after discontinuation of Isotretinoin 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 Warnings and Precautions).

INTERACTIONS

Concurrent therapy with ORATANE and vitamin A must be avoided, as symptoms of hypervitaminosis A may be intensified. As tetracyclines can also cause an increase in intracranial pressure, their combination with isotretinoin is contraindicated. The effect of microdosed progesterone preparation maybe diminished by interaction with isotretinoin. Therefore, microdosed progesterone preparations or 'minipills' should not be used.

Concurrent topical therapy:
Concurrent administration of other keratolytic or exfoliative antiacne 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.

OVERDOSAGE

Although the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in cases of accidental overdose. Such symptoms are reversible. Nevertheless, evacuation of the stomach may be indicated in the first few hours after overdosage.

PHARMACEUTICAL PRECAUTIONS

Protect from light and moisture. Store below 30 °C.
ORATANE 5 mg capsules: Shelf life of two years. ORATANE 10 mg and 20 mg capsules: Shelf life of three years.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

ORATANE 5 mg capsules: Blister pack of 60 capsules. ORATANE 10 mg and 20 mg capsules: Starter packs of 15 capsules and blister pack of 60 capsules. ORATANE 20 mg has also been approved for sale in Malaysia in a pack size of 30 capsules.

COMPOSITION

Active: Isotretinoin. {[13-cis retinoic acid] (2Z, 4E, 6E, 8E)-3,7- dimethyl-9- (2,6,6-trimethylcyclohexen-1-yl) nona-2,4,6,8- tetraenoic acid} Molecular formula C20H28O2. Capsule content excipients: Soya oil, dl-α-tocopherol, Disodium edetate, Butylated hydroxyanisole, vegetable oil hydrogenated, partly hydrogenated Soya oil, and yellow Beeswax.
Capsule shell excipients: Gelatine, Glycerol, and 70% Sorbitol solution. All capsule shells contain Ponceau 4R (CI 16255) and Titanium dioxide. The 10 mg capsule shell also contains iron oxide black (CI77499). The 20 mg capsules contain indigotin (CI73015).

NAME AND ADDRESS

Manufactured by:
Swiss Caps AG
Husenstrasse 35
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Packed by:
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***Oratane is a registered trademark in New Zealand and other countries.**

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310100

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