PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE

ORATANE 10 mg

ORATANE 20 mg

ORATANE 40 mg

ORATANE 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.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ORATANE 10 mg: Each soft gelatin capsule contains 10 mg isotretinoin.

ORATANE 20 mg: Each soft gelatin capsule contains 20 mg isotretinoin.

ORATANE 40 mg: Each soft gelatin capsule contains 40 mg isotretinoin.

All strengths contain DL-alpha-tocopherol 1,56 % *w/w* and butylhydroxyanisole 0,06 % *w/w* as antioxidants.

Excipients with known effect:

All strengths contain soya-bean oil.

All strengths contain sorbitol liquid (non-crystallizing):

ORATANE 10 mg: 7, 58 mg/capsule

ORATANE 20 mg: 24,26 mg/capsule

ORATANE 40 mg: 23,75 mg/capsule

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft gelatin capsules

ORATANE 10 mg: Light violet coloured, oval, soft gelatin capsule, containing a yellow/orange opaque

viscous suspension.

ORATANE 20 mg: Maroon coloured, oval, soft gelatin capsule, containing a yellow/orange opaque viscous suspension.

ORATANE 40 mg: A light orange coloured, oval, soft gelatin capsule, containing a yellow/orange, opaque, viscous liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe recalcitrant nodular acne: Oratane 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, ORATANE 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 Oratane.

4.2 Posology and method of administration

The initial diagnosis and prescription of Oratane 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 Oratane 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 Oratane 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:

ORATANE should not be given to breastfeeding women. ORATANE causes foetal malformations.
These foetal malformations have been documented and include hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent auditory canals), microphthalmia, cardiovascular abnormalities, facial dysmorphia, thymus gland abnormalities, parathyroid hormone deficiency and cerebellar malformations. There is also an increased risk of spontaneous abortion.
ORATANE 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 ORATANE, following the guidelines. It is recommended that two reliable forms of contraception be used simultaneously.

ORATANE is contraindicated in women of childbearing potential unless the patient meets all the following conditions:

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

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

- She must be warned of the possibility of contraception failure.

- She must confirm that she has understood the precautions.

- She must be reliable in understanding and carrying out instructions.

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

- She must use effective contraception, without interruption, for one month prior to therapy, the duration of therapy and for one month after discontinuation of therapy. Additional methods of contraception may be advised, particularly in the first cycle of hormonal contraception.

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

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

- In the event of relapse treatment, she must use the same uninterrupted and effective contraceptive measures, one month prior to, during, and for one month after ORATANE 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 ORATANE 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 ORATANE therapy.

In order to assist prescribing doctors and patients in avoiding foetal exposure to isotretinoin, the manufacturer provides a Pregnancy Prevention Program 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

- Doctor's guide to prescription

- Doctor's checklist for prescription to females

The pregnancy prevention information should be given to patients both verbally 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.

Oratane is also contraindicated in:

- Hypersensitivity to isotretinoin or to any of the ingredients of Oratane (see section 6.1).
- Oratane contains soya-bean oil. Therefore, Oratane is contraindicated in patients allergic to peanut or soya.
- Pre-existing hypervitaminosis A.
- Hepatic and renal insufficiency.
- Patients with excessively elevated blood lipid values.
- Concurrent therapy with tetracyclines (see section 4.5).

4.4 Special warnings and precautions for use

Oratane is a scheduled medicine, not a cosmetic agent. It is a criminal offence to transfer it to or share it with any person not in possession of a valid prescription.

Oratane should only be prescribed by doctors experienced in the use of systemic retinoids and who understand the risk of teratogenicity associated with isotretinoin therapy. All patients should be given a copy of the patient information brochure.

Hepatitis, which may be fatal, may occur with Oratane therapy. Liver Function should be evaluated before and one month after the start of therapy with Oratane and thereafter at three-monthly intervals. Elevations of liver enzymes have been reported with Oratane therapy, some of which normalised with dosage reduction or with continued administration. If normalisation does not occur or if hepatitis is suspected during treatment, Oratane should be discontinued and the aetiology further evaluated.

Oratane should be used with caution in:

Patients with a history of depression - Oratane may cause depression, psychosis and rarely, suicidal ideation and suicide. Patients should be monitored for signs of depression and referred for appropriate treatment.

Hypercholesterolaemia and patients with a tendency to develop hypertriglyceridaemia (e.g. those with diabetes mellitus, obesity, alcoholism or a family history of hypertriglyceridaemia) – Blood lipid determinations should be performed before therapy with Oratane and at regular intervals until the lipid response to Oratane is established, usually within one month of therapy. Approximately 25 % of patients experience a reversible elevation in plasma triglycerides, 15 % a reversible decrease in HDL cholesterol and 7 % a reversible increase in total cholesterol.

Diabetes mellitus – Frequent determinations of blood glucose levels are recommended.

Oratane therapy has been associated with:

Pseudotumour cerebri (benign intracranial hypertension) – Early signs and symptoms include papilloedema, headache, nausea, vomiting and visual disturbances. Patients presenting with these symptoms should be screened for papilloedema and, if present, discontinue therapy with Oratane. The patient should be referred to a neurologist.

Visual impairment - Corneal opacities have occurred, especially with high doses. Patients experiencing visual difficulties should stop therapy and have an ophthalmological examination. A number of cases of

decreased night vision have been reported. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night.

Acute pancreatitis - Has been reported and may be associated with serum triglycerides in excess of 800 mg/dl.

Skeletal: Skeletal hyperostosis - A higher prevalence of skeletal hyperostosis has been reported. Premature closure of the epiphysis may occur.

Inflammatory bowel disease - Patients experiencing abdominal pain, rectal bleeding or severe diarrhoea should stop therapy with Oratane.

Other precautions:

Intolerance to contact lenses may occur.

Patients should be advised not to donate blood during and for 1 month after stopping therapy with Oratane.

Excessive dermabrasion should be avoided in patients taking Oratane and for a period of 5 to 6 months after treatment because of the risk of hypertrophic scarring in atypical areas. Wax epilation should be avoided during therapy and for 5 to 6 months after therapy.

High Risk Patients: In patients with diabetes, obesity, alcoholism or a lipid metabolism disorder undergoing treatment with Oratane, 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 Oratane therapy.

Oratane contains sugar (sorbitol):

ORATANE 10 mg: 7,58 mg/capsule

ORATANE 20 mg: 24,26 mg/capsule

ORATANE 40 mg: 23,75 mg/capsule

Sorbitol is a source of fructose. Patients with rare hereditary problems of fructose intolerance (HFI) should not take Oratane.

In quantities of 140 mg/kg/day and more, sorbitol may cause gastrointestinal discomfort and mild laxative effect.

Oratane contains soya-bean oil and is contra-indicated in patients allergic to peanuts or soya (see section 4.3).

4.5 Interaction~~s~~ with other medicines and other forms of interaction

Concurrent use of Oratane with vitamin A should be avoided. Patients should be advised against taking supplements containing vitamin A to avoid additive toxic effects from hypervitaminosis A.

Concurrent use of Oratane with tetracyclines is contraindicated. Cases of benign intracranial hypertension (pseudotumor cerebri) have been reported with concomitant use (see section 4.3).

Concomitant therapy of Oratane and keratolytic or exfoliative anti-acne agents is not indicated.

Adjuvant therapy with mild topical preparations may be given, if required.

Radiation therapy or ultraviolet therapy should not be undertaken during therapy with Oratane.

No interactions between Oratane and oral contraceptives have been reported.

4.6 Fertility, pregnancy and lactation

See section 4.3 Contraindications

Pregnancy is an absolute contraindication to treatment with Oratane. If pregnancy does occur in spite of the detailed precautions during treatment with Oratane 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

ORATANE is not known for causing drowsiness.

Patients should be advised to be cautious if they feel dizzy, tired or drowsy while using Oratane during daytime.

A number of cases of decreased night vision have occurred during Oratane therapy and in some 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

Summary of the reported safety profile

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

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

Tabulated list of adverse events

System Organ Class	Incidence	Adverse events
Infections and Infestations	Less frequent	Gram positive (mucocutaneous) Bacterial infection
Blood and lymphatic system disorders	Frequent	Anaemia, increased red blood cell sedimentation rate, thrombocytopenia, thrombocytosis, neutropenia
	Less frequent	Lymphadenopathy
Immune system disorders	Less frequent	Allergic skin reaction, anaphylactic reactions, hypersensitivity
Metabolism and nutrition disorders	Less frequent	Diabetes mellitus, hyperuricaemia
Psychiatric disorders	Less frequent	Depression, aggravated depression, aggressive tendencies, anxiety, mood alterations, abnormal behaviour, psychotic disorder, suicidal ideation, suicide, suicide attempt
Nervous system disorders	Frequent	Headache
	Less frequent	Benign intracranial hypertension, convulsions, drowsiness
Eye disorders	Frequent	Blepharitis, conjunctivitis, dry eyes, eye irritation
	Less frequent	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	Less frequent	Impaired hearing
Vascular disorders	Less frequent	Vasculitis (e.g. Wegener's (eosinophilic) granulomatosis allergic vasculitis)

Respiratory, thoracic and mediastinal disorders	Frequent	Nasopharyngitis, epistaxis, nasal dryness
	Less frequent	Bronchospasm (particularly in patients with asthma), hoarseness
Gastrointestinal disorders	Less frequent	Colitis, ileitis, dry throat, gastrointestinal haemorrhage, haemorrhagic diarrhoea and inflammatory bowel disease, nausea, pancreatitis (see section 4.4)
Hepatobiliary disorders	Frequent	Increased transaminase
	Less frequent	Hepatitis
Skin and Subcutaneous tissue disorders	Frequent	Cheilitis, dermatitis, dry skin, localised exfoliation, pruritus, erythematous rash, skin fragility (risk of frictional trauma)
	Less frequent	Alopecia, Acne fulminans, aggravated acne (acne flare), erythema (facial), exanthema, hair disorders, hirsutism, nail dystrophy, paronychia, photosensitivity reaction, pyogenic granuloma, skin hyperpigmentation, increased sweating
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, myalgia, back pain (particularly adolescent patients)
	Less frequent	Arthritis, calcinosis (calcification of ligaments and tendons), epiphyses premature fusion, exostosis, (hyperostotis), reduced bone density, tendonitis
Renal and urinary disorders	Less frequent	Glomerulonephritis
General disorders and administration site conditions	Less frequent	Increased formation of granulation tissue, malaise

Investigations	Frequent	Increased blood triglicerides, decreased high density lipoprotein, increased blood cholesterol, increased blood glucose, haematuria, proteinuria
	Less frequent	Increased blood creatine phosphokinase

Post Marketing

During the post-marketing period, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with Oratane, (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.

Reporting of suspected adverse reactions

If you get side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects to Acino Pharma via drugsafety_za@acino.swiss

OR

to SAHPRA via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

By reporting side effects, you can help provide more information on the safety of Oratane.

4.9 Overdose

See section 4.8 and section 4.4.

Symptoms of overdose:

Signs of hypervitaminosis A may occur in case of overdose.

Treatment of overdose:

Treatment is symptomatic and supportive. Evacuation of the stomach may be indicated in the first few hours after overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class:

A 13.4.2 Dermatological preparations – other

Pharmacotherapeutic group: Retinoid for treatment of acne, ATC code:

Mechanism of action

Isotretinoin is a synthetic stereoisomer of all-trans retinoic acid (tretinoin). The exact mechanism of action of isotretinoin is unknown. The action of isotretinoin 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 of isotretinoin can be predicted from single-dose data on the basis of linear pharmacokinetics. This property also provides some evidence that the activity of hepatic 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 of isotretinoin, peak plasma concentrations ranged from 167 ng/ml to 459 ng/ml (mean 256 ng/ml). Peak plasma concentrations were achieved within 1 - 6 hours (mean 3,2 hours) in healthy volunteers. In acne patients peak concentrations were ranged from 98 ng/ml to 535 ng/ml (mean 262 ng/ml) and occurred at 2 - 4 hours after administration (mean 2,9 hours). The mean ± 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 patients.

Distribution

Isotretinoin is 99,9 % bound to plasma proteins. Albumin appears to be the major binding protein. Steady state blood concentrations ($C_{min.ss}$) of isotretinoin in patients with acne treated with 40 mg twice a day ranged from 120 - 200 ng/ml. The concentrations 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.

Since isotretinoin and tretinoin (all-trans retinoic acid) are reversibly metabolised, the metabolism of tretinoin is linked with that of isotretinoin. Evidence of first pass metabolism of isotretinoin has been shown. 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 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 CYP2Ea contribute to the metabolism of isotretinoin. CYP26 is also known to metabolise retinoids.

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 isotretinoin 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 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

ORATANE 10 mg:

Capsule fill:

DL-alpha-tocopherol

beeswax, yellow

butylhydroxyanisole

disodium edetate (as dihydrate)

hydrogenated vegetable oil

soya-bean oil, partly hydrogenated

soya-bean oil, refined

Capsule shell:

gelatin

glycerol

purified water

sorbitol liquid (non-crystallizing)

titanium dioxide

iron oxide black

Ponceau 4R

ORATANE 20 mg:

Capsule fill:

DL-alpha-tocopherol

beeswax, yellow

butylhydroxyanisole

disodium edetate (as dihydrate)

hydrogenated vegetable oil

soya-bean oil, partly hydrogenated

soya-bean oil, refined

Capsule shell:

gelatin

glycerol

sorbitol liquid (non-crystallizing)

titanium dioxide

Indigotine lacquer

Ponceau 4R

ORATANE 40 mg:

Capsule fill:

DL-alpha-tocopherol

beeswax, yellow

butylhydroxyanisole

disodium edetate (as dihydrate)

soya-bean oil, hydrogenated

soya-bean oil, partly hydrogenated

soya-bean oil, refined

Capsule shell:

gelatin

glycerol

sorbitol liquid (non-crystallizing)

Sunset yellow E110

titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 30 °C.

Protect from light.

Keep blisters in outer carton until required for use.

Do not refrigerate or freeze the product.

6.5 Nature and contents of the container

ORATANE 10 mg and **20 mg:** PVC/PVDC/Aluminium blister strips containing 15 capsules packed in

pack size of 60 capsules within an outer carton.

ORATANE 40 mg: PVC/PVDC film or PVC/PCTFE film blister strips sealed with aluminium foil containing 10 capsules, packed in pack size of 30 capsules within an outer carton.

6.6 Special precautions for disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 – 16th Road

Midrand

1685

8. REGISTRATION NUMBERS

ORATANE 10 mg: 35/13.4.2/0375

ORATANE 20 mg: 35/13.4.2/0376

ORATANE 40 mg: 42/13.4.2/0460

9. DATE OF FIRST AUTHORISATION

ORATANE 10 mg: 25 April 2003

ORATANE 20 mg: 25 April 2003

ORATANE 40 mg: 1 October 2015

10. DATE OF REVISION OF THE TEXT

Date of current approved package insert: 09 October 2021

Manufactured by:

SWISS CAPS AG (Aenova)

Husenstrasse 35

CH-9533, Kirchberg

Switzerland

Prescription Only Medicine
Oratane 10 mg: Registration numbers per country;
Botswana (S2): BOT1402526 Tanzania: TAN 20 HM 0430 Uganda: NDA/MAL/HDP/10379
Oratane 20 mg: Registration numbers per country:
Botswana (S2): BOT1402527 Tanzania: TAN 20 HM 0443 Uganda: NDA/MAL/HDP/10380
Oratane 40 mg: Registration numbers per country:
Ghana: FDA/SD.223-091436 Namibia (NS3): 18/13.4.3/0016 Tanzania: TAN 21 HM 0038 Uganda: NDA/MAL/HDP/10381

OR

Douglas Manufacturing Ltd

Corner Te Pai Place and Central Park Drive;

Lincoln;

Auckland 0610,

New Zealand

Prescription Only Medicine
Oratane 10 mg: Registration numbers per country;
Ghana: FDA/SD.223-091434 Namibia (NS3): 04/13.4.2/1717
Oratane 20 mg: Registration numbers per country:
Ghana: FDA/SD.223-091435 Namibia (NS3): 04/13.4.2/1718

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