PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE

ORATANE 5 mg

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 5 mg: Each soft gelatin capsule contains 5 mg isotretinoin.

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 sugar (sorbitol liquid (non-crystallizing)):

ORATANE 5 mg: 5 mg/capsule

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 5 mg: Faint pinkish-cream to cream coloured, oval, soft gelatin capsule, containing a yellow/orange, opaque viscous liquid.

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

Paediatric population

Oratane should not be used for treatment of prepubertal acne and is not recommended in children less than 12 years of age due to lack of data on efficacy and safety.

Adults including adolescents and the elderly

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. The 5 mg capsule may be used if necessary, to adjust the reduced dosage appropriately. Note that the 5 mg capsule alone should not be used to initiate therapy as the starting dose cannot be achieved with a single 5 mg capsule daily.

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 medicines 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 medical practitioner 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. Careful consideration must be given in each individual case to the efficacy of the contraceptive methods chosen, 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 strongly 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 medical practitioners 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

- Medical practitioner's guide to prescription

- Medical practitioner'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 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 medicine. 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 medical practitioners 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 isotretinoin as in 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, reduction of dose or discontinuation of Oratane therapy should be considered and the aetiology further evaluated

Oratane should be used with caution in:

- Patients with a history of depression - Depression, aggravated depression, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with Oratane (see section 4.8). Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of Oratane may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.
- 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 and also at the end of treatment. The serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment. The changes in serum lipids may resolve in response to dietary measures. Approximately 25 % of patients receiving isotretinoin as in Oratane experience an elevation in plasma triglycerides, 15 % a decrease in high-density lipoproteins

(HDL) cholesterol and 7 % an increase in total cholesterol. These effects on triglycerides, HDL and cholesterol were reversible upon cessation of isotretinoin as in Oratane therapy.

- Diabetes mellitus – Frequent determinations of blood glucose levels are recommended. New cases of diabetes mellitus have been diagnosed during isotretinoin as in Oratane therapy.

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. Supplementary treatment with tetracyclines is contraindicated (see section 4.3).

- Visual impairment

    - Corneal Opacities: Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. Due to the possible occurrence of keratitis, patients with dry eyes should be monitored. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment. Patients experiencing visual difficulties should be referred for an expert ophthalmological examination and withdrawal of Oratane considered.
    - Decreased night vision: Decreased night vision may occur during Oratane therapy, and may persist after discontinuation of therapy, (see section 4.8). Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. Visual problems should be carefully monitored. Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion. Withdrawal of Oratane may be necessary.

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

section 4.8).

- Mulsculo-skeletal and connective tissue disorders - Myalgia, arthralgia and increased serum creatine phosphokinase values have been reported in patients receiving isotretinoin as in Oratane, particularly in those undertaking vigorous physical activity.
    - *Hyperostosis:* In clinical trials for disorders of keratinisation with a mean dose of 2,24 mg/kg/day, a high prevalence of skeletal hyperostosis was noted. Additionally, skeletal hyperostosis was noted in 6 of 8 patients in a prospective study of disorders of keratinisation. Skeletal hyperostosis has also been observed by X-rays in prospective studies of nodular acne patients treated with a single course of therapy at recommended doses.
    - *Premature epiphyseal closure:* Bone changes including premature epiphyseal closure and calcification of tendons and ligaments have occurred after several years of administration at very high doses for treating disorders of keratinisation. The dose levels, duration of treatment and total cumulative dose in these patients generally far exceeded those recommended for the treatment of acne. Therefore, a careful evaluation of the risk/benefit ratio should be carried out in every patient.
- Gastrointestinal disorders – Isotretinoin as in Oratane 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 Oratane immediately.

Pregnancy and lactation

Oratane IS TERATOGENIC.

Females of childbearing potential, as well as female patients who normally do not employ contraception because of a history of infertility, should be instructed that they must not be pregnant when Oratane therapy is initiated, and that they should use effective contraception while taking Oratane without any interruptions for 1 month prior to therapy, the duration of therapy and for 1 month after discontinuation of therapy. It is recommended that two reliable forms of contraception be used simultaneously. Micro-dosed progesterone preparation (minipills) may be an inadequate method of contraception during Oratane therapy. Although other hormonal contraceptives are effective, there have been reports of pregnancy from women who have used oral contraceptives, as well as injectable/implantable contraceptive medicines.

These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with Oratane.

Therefore it is important that women of childbearing potential use two effective forms of contraception simultaneously. They should also sign a Consent Form prior to beginning Oratane therapy (see boxed section 4.3).

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

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

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The prescriber must ensure that:

- The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.
- The patient has used at least one and preferably two methods of effective contraception

including a barrier method for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment.

- Negative pregnancy test results have been obtained before, during and 5 weeks after the end of treatment. The dates and results of pregnancy tests should be documented.

Pregnancy testing:

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

Prior to starting therapy:

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

A medically supervised pregnancy test should also be performed during the consultation when isotretinoin is prescribed or in the 3 days prior to the visit to the prescriber, and should have been delayed until the patient had been using effective contraception for at least 1 month. This test should ensure the patient is not pregnant when she starts treatment with Oratane.

Follow-up visits:

Follow-up visits should be arranged at 28 day intervals. The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient's sexual activity and recent menstrual history (abnormal menses, missed periods or amenorrhoea). Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

End of treatment:

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

Prescribing and dispensing restrictions:

Prescriptions of Oratane for women of childbearing potential should be limited to 30 days of treatment

and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of Oratane should occur on the same day. Dispensing of Oratane should occur within a maximum of 7 days of the prescription.

Male patients:

The available data suggest that the level of maternal exposure from the semen of the patients receiving 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 medicine with anyone, particularly not females.

Educational material

Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the doctor to all patients, both male and female.

Other precautions:

- Patients should be instructed never to give Oratane to another person and to return any unused capsules to their pharmacist at the end of treatment.
- Patients should be advised not to donate blood during and for 1 month after stopping therapy with Oratane because of the potential risk to the foetus of a pregnant transfusion recipient.
- Skin and subcutaneous tissues disorders - Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually within 7 - 10 days, and usually does not require dose adjustment.

  Exposure to intense sunlight or to UV rays should be avoided. Where necessary a sun protection product with a high protection factor of at least SPF 15 should be used.

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

  Concurrent administration of Oratane with topical keratolytic or exfoliative anti-acne medicines should be avoided as local irritation may increase. Patients should be advised to use a skin

moisturising ointment or cream and a lip balm from the start of treatment as Oratane is likely to cause dryness of the skin and lips.

There have been post-marketing reports of severe skin reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis) associated with isotretinoin as in Oratane use. These events may be serious and result in death, life threatening events, hospitalisation, or disability. Patients should be monitored closely for severe skin reactions and Oratane should be discontinued if these occur.

- Renal insufficiency - Renal insufficiency and renal failure do not affect the pharmacokinetics of Oratane. Therefore, Oratane can be given to patients with renal insufficiency. However, it is recommended that patients are started on a low dose and titrated up to the maximum tolerated dose.
- Allergic reactions - Anaphylactic reactions have been reported, in some cases after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.
- 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.

Paediatric population

Safety and effectiveness in children under the age of 12 years have not been established.

Information on excipients

Oratane contains sugar (sorbitol):

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

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

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 Interactions 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 medicines 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 isotretinoin as in Oratane and oral contraceptives have been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy

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).

Breastfeeding

The passage of isotretinoin into human milk is very likely. Due to the potential of adverse effects in the child exposed via mother's milk, Oratane is contraindicated during breastfeeding (see section 4.3).

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 as in Oratane.

4.7 Effects on ability to drive and use machines

Isotretinoin as in ORATANE may cause drowsiness, dizziness and visual disturbances which may have

influence on the ability to drive and use machines.

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.

Therefore, they should not drive or operate machines until they know how treatment with Oratane affects them.

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	Frequent	Headache

disorders	Less frequent	Benign intracranial hypertension (pseudotumour cerebri), convulsions, drowsiness, dizziness
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, visual disturbances.
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

	Frequency unknown	Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis
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
	Frequency unknown	Rhabdomyolysis: often leading to hospitalisation and some fatal outcome, have been reported, particularly in those undertaking vigorous physical activity.
Reproductive system and breast disorders	Frequency unknown	Sexual dysfunction including erectile dysfunction and decreased libido, gynaecomastia, vulvovaginal dryness.
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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

See section 4.8 and section 4.4.

Symptoms of overdose:

Isotretinoin is a derivative of vitamin A. Signs of hypervitaminosis A may occur in case of overdose. Manifestations of acute vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability, and pruritus. Signs and symptoms of accidental overdosage with Oratane would probably be similar.

Treatment of overdose:

Treatment is symptomatic and supportive.

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:

D10B A01

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.

Biotransformation

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 5 mg:

Capsule Fill:

all-rac-alpha-tocopherol

beeswax, yellow

butylhydroxyanisole

disodium edetate (as dihydrate)

hydrogenated vegetable oil

soya-bean oil, partly hydrogenated

soya-bean oil, refined

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 5 mg: Capsules are packed into PVC/PVDC film with Aluminium backing blister strips of 30 capsules within an outer carton.

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 5 mg: 43/13.4.2/0746

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 5 mg: 29 November 2022

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: 29 November 2022

Prescription Only Medicine

ORATANE 10 mg:

Registration numbers per country:	
Ghana: FDA/SD.193-11981 Kenya: Mauritius: R9944/02/14 Namibia: 04/13.4.2/1717: Scheduling status: NS3	Nigeria: Tanzania: TAN 20 HM 0430 Uganda: Botswana: BOT1402526: Sceduling status: N2

ORATANE 20 mg:

Registration numbers per country:	
Ghana: FDA/SD.193-11982 Kenya: Mauritius: R9945/02/14	Nigeria: Tanzania: TAN 20 HM 0443 Uganda:

Namibia: 04/13.4.2/1718: Scheduling status: NS3	Botswana BOT1402527: Scheduling status: S2

ORATANE 40 mg:

Registration numbers per country:	
Ghana: FDA/SD.193-11983 Kenya: Mauritius: E13091/03/2019 Namibia: 18/13.4.3/0016: Scheduling status: NS3	Nigeria: Tanzania: TAN 21 HM 0038 Uganda: