

New Zealand Data Sheet

1. PRODUCT NAME

ORATANE® 5 mg soft gelatin capsule
ORATANE® 10 mg soft gelatin capsule
ORATANE® 20 mg soft gelatin capsule
ORATANE® 30 mg soft gelatin capsule
ORATANE® 40 mg soft gelatin capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ORATANE 5 mg soft gelatin capsule contains 5 mg of isotretinoin.
Each ORATANE 10 mg soft gelatin capsule contains 10 mg of isotretinoin.
Each ORATANE 20 mg soft gelatin capsule contains 20 mg of isotretinoin.
Each ORATANE 30 mg soft gelatin capsule contains 30 mg of isotretinoin.
Each ORATANE 40 mg soft gelatin capsule contains 40 mg of isotretinoin.

Excipient(s) with known effect

ORATANE soft gelatin capsules contain soya oil and sorbitol.

For the full list of excipients, *see Section 6.1.*

3. PHARMACEUTICAL FORM

ORATANE 5 mg capsules: Soft gelatin oval opaque white capsules, approximately 8 mm in length and 5 mm in diameter.

ORATANE 10 mg capsules: Soft gelatin oval opaque violet capsules, approximately 10 mm in length and 7 mm in diameter.

ORATANE 20 mg capsules: Soft gelatin oval opaque maroon capsules, approximately 13 mm in length and 8 mm in diameter.

ORATANE 30 mg capsules: Soft gelatin oval opaque pink capsules, approximately 12 mm length and 8 mm in diameter.

ORATANE 40 mg capsules: Soft gelatin oval opaque light orange capsules, approximately 13 mm length and 8 mm in diameter.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Severe forms of nodulo-cystic acne which are resistant to therapy, particularly cystic acne and acne conglobata, especially when the lesions involve the trunk.

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

4.2. Dose and method of administration

Dose

Patient response to isotretinoin is dose-related and varies from case to case. This necessitates adapting the dosage to individual needs according to severity of the clinical picture and side effects. With a dosage of between 0.1 and 1.0 mg/kg daily over 12-16 weeks, it is generally possible to achieve a considerable improvement or complete healing. The daily dose is taken with meals; low doses once daily and higher amounts as a single dose or in several doses spread over the day.

Initial treatment

As a rule, therapy is started with 0.5 mg/kg daily and maintained for 2 to 4 weeks until the patient's response is clear. Initially, the acne may be aggravated for a short period.

A cumulative dose of 120 mg/kg per treatment has been documented to increase remission rates and prevent relapse. The therapy duration in individual patients therefore varies as a function of the daily dose. Complete remission of the acne is often achieved by a therapy course of 16-24 weeks. In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequence of longer therapy duration.

Follow-up Treatment (Maintenance Dose)

In patients who respond well to isotretinoin, treatment should be continued with a dosage of 0.5 mg/kg daily. With patients who show signs of intolerance during the initial therapy, the daily dosage should be reduced to 0.1-0.2 mg/kg. Where response to the initial dosage is slight, and in particularly severe cases, the daily dosage may be increased to 1 mg/kg provided the medicine is well tolerated.

The maintenance dose is administered for a period of 12 weeks after which the first stage of therapy is generally terminated. After discontinuation of treatment, often a further improvement is observed which may last from a few weeks to several months. There should, therefore, be an interval of at least eight weeks before restarting treatment. In the event of recurrence of the acne, treatment should be resumed on the above lines, bearing in mind that recurrences may respond to a lower dosage.

Concurrent Adjuvant Treatment

As a rule, this is not indicated. It is advisable to discontinue antimicrobials before beginning treatment with isotretinoin (refer to section 4.8). Concomitant radiation (ultraviolet) therapy and exposure to sunlight should also be avoided. Concomitant topical therapy of a mild nature may, however, be carried out.

Special populations

Patients with renal impairment

If appropriate, treatment should be started at a lower dose (e.g. 10 mg/day) and afterwards individually adjusted according to tolerability (refer to section 4.3).

Paediatric population

Long term use in children under 13 years should be avoided because of a risk of premature epiphyseal closure (refer to section 4.4).

Method of Administration

The daily dose is taken with meals.

4.3. Contraindications

- Isotretinoin is contraindicated in women who are pregnant, (refer to section 4.6), or who may become pregnant while undergoing treatment.
- Isotretinoin is contraindicated in women of childbearing potential unless the female patient meets *all* of the conditions listed in Section 4.4- Women of childbearing potential
- Isotretinoin is also contraindicated in patients with hypersensitivity to isotretinoin or to any of the excipients listed in Section 6.1.
- Isotretinoin is also contraindicated in patients with
 - hepatic and renal insufficiency
 - hypervitaminosis A
 - excessively elevated blood lipid values.

4.4. Special warnings and precautions for use

Pregnancy Prevention

Isotretinoin is highly TERATOGENIC.

It 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. 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.

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.

Women of childbearing potential

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

- She has severe disfiguring cystic acne resistant to standard therapies.
- She must be reliable in understanding and carrying out instructions.
- She is capable of complying with the mandatory contraceptive measures.
- She is informed by the physicians of the hazards of becoming pregnant during and 1 month after treatment with isotretinoin and she is warned of the possibility of contraceptive failure.
- She confirms that she has understood the warnings.
- She has a negative pregnancy test within two weeks prior to beginning therapy. Monthly repetition of pregnancy testing is recommended.
- She must use effective contraception without any interruption for 1 month before beginning isotretinoin therapy, during therapy and for 1 month following discontinuation of therapy. Use of two complementary forms of contraception including a barrier method should be used. Micro-dosed progesterone only preparations (minipills) are an inadequate method of contraception during isotretinoin therapy.
- She starts isotretinoin therapy only on the second or third day of the next menstrual period.
- In the event of relapse treatments, she must also use the same uninterrupted and effective contraceptive measures 1 month prior to, during and for 1 month after isotretinoin therapy.
- She must fully understand the precautions and confirm her understanding and her willingness to comply with reliable contraceptive measures as explained to her.

Even female patients, who normally do not employ contraception because of a history of infertility, should be advised to do so while taking isotretinoin, following the above guidelines.

Should pregnancy occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe malformation of the foetus (involving in particular the central nervous system, the heart and the large blood vessels). If pregnancy does occur, the doctor and patient should discuss the advisability of continuing the pregnancy.

Major human foetal abnormalities related to isotretinoin administration have been documented, including hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent external auditory canals), microphthalmia, cardiovascular abnormalities, facial dysmorphism, thymus gland abnormalities, parathyroid hormone deficiency and cerebellar malformation.

There is also an increased risk of spontaneous abortion.

Male Patients

The available data suggest that the level of maternal exposure from the semen of patients receiving isotretinoin, is not of sufficient magnitude to be associated with the teratogenic effect

of isotretinoin.

Male patients should be reminded that they must not share their medication with anyone, particularly not females.

Hypersensitivity reactions

Hypersensitivity reactions may occur in susceptible individuals.

Hepatic impairment

Several cases of clinical hepatitis have been noted which are considered to be possibly or probably isotretinoin therapy. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials, some of which normalised with dosage reduction or continued administration of the drug. If normalisation does not readily occur or if hepatitis is suspected during treatment with isotretinoin, discontinue treatment with isotretinoin and the etiology further investigated.

Psychiatric disorders

Depression psychotic symptoms and rarely suicide attempts and suicide have been reported in patients treated with isotretinoin (refer to section 4.8). Although a causal relationship has not been established particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary.

Blood donation

Blood donation to women of childbearing age by patients being treated or recently treated (one month) with isotretinoin is contraindicated.

Skin and subcutaneous tissues disorders

Acute exacerbation of acne is generally seen during the initial period of treatment; but this subsides with continued treatment, usually within 7-10 days, and usually does not require dose adjustments.

Aggressive dermabrasion and cutaneous laser 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 and more rarely hyper- or hypopigmentation in treated 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.

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

Patients should be advised to use a skin-moisturising ointment or cream and a lip balm from the start of treatment as isotretinoin 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 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 discontinuation of isotretinoin should be considered if warranted.

Benign intracranial hypertension

Isotretinoin use has been associated with a number of cases of benign intracranial hypertension (pseudotumor cerebri), some of which involved the concomitant use of tetracyclines, *See Section 4.8*. Supplementary treatment with tetracyclines is, therefore, contraindicated. Early signs and symptoms of benign intracranial hypertension include papilloedema, headache, nausea and vomiting, and visual disturbances.

Patients who develop benign intracranial hypertension should discontinue isotretinoin immediately.

Eye disorders

Dry eyes, corneal opacities, conjunctivitis, blepharitis, decreased night vision and keratitis usually resolve after discontinuation of therapy. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Patients, particularly those with dry eyes, should be monitored for the development of keratitis.

Patients experiencing visual difficulties should be referred for an expert ophthalmological examination and withdrawal of isotretinoin considered. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.

Corneal opacities have occurred in patients receiving isotretinoin for acne and more frequently when higher drug dosages were used in patients with disorders of keratinisation. All isotretinoin patients experiencing visual difficulties should discontinue the drug and have an ophthalmological examination.

Hearing impairment

Impaired hearing has been reported in patients taking isotretinoin. Hearing impairment can be unilateral or bilateral, and symptoms include tinnitus, impaired hearing at certain frequencies and deafness. In some cases, hearing impairment has been reported to persist after therapy has been discontinued. Anyone who experiences these symptoms should immediately seek medical advice; the drug should be ceased, and the patient should undergo urgent formal audiology assessment.

Hepatobiliary disorders

Rises in alanine and aspartate aminotransferase enzymes (ALT and AST) have been reported. Liver function tests, especially AST and blood lipids should be checked before and one month after the start of treatment and subsequently at monthly intervals during therapy and at the end of treatment. When transaminase levels exceed the normal levels, reduction of the dose

or discontinuation of treatment may be necessary.

Lipid metabolism

Isotretinoin causes elevation of serum triglycerides and cholesterol as well as a decrease in H.D.L., which appear to be related to duration of treatment and are reversible on cessation of treatment. The degree of elevation may also be dose dependent although this has not been conclusively established.

At doses of greater than 1 mg/kg/day, approximately one in four patients have been found to develop elevated triglycerides while taking isotretinoin. At lower doses triglyceride levels elevated above the normal range are uncommon.

Some patients have been able to reverse triglyceride elevations by weight reduction and restriction of dietary fat and alcohol while continuing to take isotretinoin. Serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment.

Acute pancreatitis, which is potentially fatal, sometimes associated with serum triglycerides levels > 8g/L, has been reported. Hence, isotretinoin should be discontinued if uncontrolled hypertriglyceridemia or symptoms of pancreatitis occur.

Serum lipids (fasting value) should be determined one month prior to therapy and again after about 4 weeks of therapy and subsequently at three-month intervals unless more frequent monitoring is clinically indicated.

High risk patients

Predisposing factors such as a family history of lipid metabolism disorders, obesity, alcoholism, diabetes and smoking should be assessed. In high risk patients (with diabetes, obesity, alcoholism or lipid metabolism disorder) undergoing treatment with isotretinoin, more frequent checks of serum values for lipids and/or blood glucose may be necessary.

Musculo-skeletal and connective tissue disorders

Myalgia and arthralgia may occur and may be associated with reduced tolerance to vigorous exercise (refer to section 4.8). Isolated instances of raised serum CPK values have been reported in patients receiving isotretinoin, particularly those undertaking vigorous physical activity. In clinical trials of disorders of keratinisation with a mean dose of 2.24 mg/kg/day a high prevalence of skeletal hyperostosis was noted. Bone changes including premature epiphyseal closure and calcifications of tendons and ligaments have occurred after administration of high doses for long periods 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.

Minimal 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.

Isotretinoin may be associated with growth retardation in prepubertal children.

Due to the possible occurrence of bone changes, a careful evaluation of the risk/benefit ratio should be carried out in every patient and isotretinoin administration should be restricted to severe cases.

Gastrointestinal disorders

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.

Allergic Reactions

Anaphylactic reactions have been rarely reported and only after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.

Effects on laboratory tests

Elevation of lipid (triglycerides and cholesterol) levels occurs with isotretinoin therapy. These are usually mild in doses less than 1 mg/kg/day and elevations above the normal range are unusual at 0.5 mg/kg/day. At doses above 1 mg/kg/day, elevation (above the normal range) occurs in 25% of patients.

These changes are seen more frequently in patients where a family history of lipid disorders, or obesity, alcohol abuse, diabetes mellitus or smoking is present. The changes are dose related and may be controlled by dietary means (including alcohol restriction) or dosage reduction.

Elevated ESR values occur in about 40% of patients treated with isotretinoin.

A rise in aspartate aminotransferase (AST) levels may occur, especially with the higher dosages of isotretinoin. Although the changes have usually been within the normal range, and may return to baseline levels despite continued treatment, significant increases have occurred in a few cases, necessitating dosage reduction or discontinuation of isotretinoin.

Certain patients receiving isotretinoin have experienced problems in the control of their blood sugar. Therefore, known or suspected diabetics should have frequent blood sugar determinations performed during isotretinoin therapy. New cases of diabetes have been diagnosed.

A small number of patients have shown proteinuria, microscopic or gross haematuria and elevated CPK.

4.5. Interaction with other medicines and other forms of interaction

Concurrent therapy with ORATANE and vitamin A must be avoided, as symptoms of hypervitaminosis A may be intensified (refer to section 4.3 and 4.8)

Cases of pseudotumour cerebri and/or papilloedema have been reported in association with the use of isotretinoin. Four out of ten of these patients had retinal hemorrhages. Symptoms appeared after 21 days to 6 months therapy with 40 to 120 mg daily. As tetracyclines or minocycline was administered in 5 out of 10 cases - both of these drugs can also an increase in intracranial pressure, their combination with isotretinoin is contraindicated, *see Section 4.4*.

No further interactions between isotretinoin and other medicines including combined oral contraceptives as recommended for pregnancy prevention have been observed to date.

Concurrent administration of other topical 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.

Since acne is an androgen-dependent disease, contraceptives containing an androgen progestational substance, such as one derived from 19-nortestosterone (norsteroid), particularly in the presence of gynaecoendocrinological problems, should be avoided.

4.6. Fertility, pregnancy and lactation

Pregnancy

Pregnancy (Category X)

Isotretinoin is highly teratogenic and must not be given to women who are pregnant (refer to section 4.3). 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 isotretinoin in any amount even for short periods. Potentially all exposed fetuses can be affected.

Breast-feeding

Owing to its lipophilicity, there is a high probability that isotretinoin is secreted into the breast milk. Isotretinoin must not be given to nursing mothers.

Fertility

In studies in 66 human males, 30 of who were patients with cystic acne, no significant changes were noted in the count or motility of spermatozoa in the ejaculate (refer to section 5.3).

4.7. Effects on ability to drive and use machines

Changes in vision, including decreased night vision, have been reported during isotretinoin therapy (refer to section 4.4 and 4.8). Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night.

4.8. Undesirable effects

Most of the adverse effects of isotretinoin are dose related with more pronounced effects occurring at doses above 1 mg/kg/day. The adverse effects may recede during continued therapy and the mucocutaneous effects were reversible with dosage reduction or discontinuation of therapy. Exacerbation of the cystic acne may occur during the initial stages of therapy.

Post marketing experiences

Hypervitaminosis A

The most frequently observed symptoms are those associated with hypervitaminosis A, dryness of the skin, in particular peeling of the palms and soles, dryness of the mucosa e.g. of the lips (cheilitis, which occurs in over 90% of patients) can be relieved by the application of a fatty ointment, dryness of the nasal mucosa which can lead to epistaxis (which is seen in up to 30% of patients), dryness of the pharyngeal mucosa (hoarseness) dryness of the eyes (conjunctivitis, reversible corneal opacities and intolerance to contact lenses).

Skin and subcutaneous tissue disorders

Exanthema, pruritus, facial erythema/dermatitis, sweating, pyogenic granuloma, paronychia, nail dystrophy and increased formation of granulation tissue, persistent hair thinning, reversible alopecia, hirsutism, acne fulminans, hyperpigmentation photosensitivity, photoallergic reactions, skin fragility. Acne flare occurs at the start of treatment and persists for several weeks

During the post-marketing period, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with isotretinoin (refer to section 4.4).

Musculo-skeletal and connective tissue disorders

Myalgia (muscle pain) with or without elevated serum CPK values (refer to section 4.4), arthralgia (joint pain), hyperostosis, arthritis, calcification of ligaments and tendons and other bone changes, reduced bone density, back pain, epiphyses, premature fusion, tendinitis.

Serious cases of rhabdomyolysis, often leading to hospitalization and some with fatal outcome have been reported, particularly in those undertaking vigorous physical activity.

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 the risk/benefit ratio should be carried out in every patient and isotretinoin administration should be restricted to severe cases.

Psychiatric disorders and Nervous system disorders

Behavioural disorders, depression, suicide attempt, suicide (refer to section 4.4), headache, increased intracranial pressure (pseudotumor cerebri) and seizures.

Eye disorders

Visual disturbances, photophobia, dark adaptation disturbances (decreased night vision), colour vision disturbances (reversible upon discontinuation), lenticular cataracts, keratitis, blurred vision, blepharitis, conjunctivitis, eye irritation, papilledema as a sign of intracranial hypertension, impaired hearing at certain frequencies.

Gastrointestinal disorders

Nausea, severe diarrhoea, inflammatory bowel disease such as colitis, ileitis, and hemorrhage have been reported to occur. Patients treated with isotretinoin, especially those with high triglyceride levels are at risk of developing pancreatitis. Fatal pancreatitis has been rarely reported (refer to section 4.4).

Hepatobiliary disorders

Transient and reversible increases in liver transaminases, some cases of hepatitis.

Respiratory, thoracic and mediastinal disorders

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

Reproductive system and breast disorders

Sexual dysfunction including erectile dysfunction and decreased libido has been reported with an unknown frequency, i.e. cannot be estimated from the available data.

Blood and lymphatic system disorders

Decrease in white blood cell count, neutropenia, disorders of red blood cell parameters (such as decrease in red blood cell count and hematocrit), elevation of sedimentation rate increase or decrease in platelet count (thrombocytopenia), anaemia, lymphadenopathy.

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), which appear to be related to duration of treatment and are reversible on cessation of treatment. The degree of elevation may also be dose dependent although this has not been conclusively established.

Haematuria and proteinuria occur rarely.

Infections

Local or systemic infections due to Gram-positive microorganisms (*Staphylococcus aureus*).

Vascular disorders

Vasculitis (for example Wegener's granulomatosis, allergic vasculitis).

Renal and urinary disorders

Glomerulonephritis, haematuria, proteinuria.

Immune system disorders

Allergic responses and systemic hypersensitivity.

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. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

Although the acute toxicity of overdosage 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Retinoids for treatment of acne; ATC code: D10B A01

Pharmacodynamic effects

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.

5.2. Pharmacokinetic properties

Absorption

There is considerable inter-individual variation in the bioavailability of oral isotretinoin. After oral administration of 80 mg (2 x 40 mg capsules) given in the fasting state peak plasma concentrations ranged from 167 to 459 nanogram/mL and mean time to peak was 3.2 hours in healthy volunteers, while in acne patients peak concentrations ranged from 98 to 535 nanogram/mL (mean 262 nanogram/mL) with a mean time to peak of 2.9 hours.

Taking isotretinoin with food increases bioavailability up to 1 ½ to 2 times greater than when taken in fasting conditions.

Distribution

Isotretinoin is extensively bound to plasma proteins (99.9 %). Albumin appears to be the major

binding protein.

Tissue Distribution in Animals: Tissue distribution of ¹⁴C- isotretinoin in rats revealed high concentrations of radioactivity in many tissues after 15 minutes, with a maximum in 1 hour, and declining to non-detectable levels by 24 hours in most tissues. After seven days, however, low levels of radioactivity were detected in the liver, ureter, adrenal, ovary and lacrimal gland.

Biotransformation

Three 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. After two 40 mg capsules of isotretinoin, maximum concentrations of the metabolite of 87 to 399 nanogram/mL occurred at 6 to 20 hours. The blood concentration of the major metabolite generally exceeded that of isotretinoin after 6 hours.

The mean +SD minimum steady-state blood concentrations of isotretinoin were 160 +19 nanogram/mL in 10 patients receiving 40 mg twice daily. After single and multiple doses, the mean ratio of areas under the curves of isotretinoin to 4-oxo-isotretinoin is 3 to 3.5.

Elimination

The terminal elimination half-life of isotretinoin ranged from 10 to 20 hours in volunteers and patients. Following an 80 mg liquid suspension oral dose of ¹⁴C-isotretinoin, ¹⁴C-activity in blood declined with a half-life of 90 hours. Relatively equal amounts of radioactivity were recovered in the urine and faeces with 65-83% of the dose recovered. The apparent half-life for elimination of the 4-oxo-metabolite ranged from 11 to 50 hours with a mean of 29 hours. This metabolite is subject to recycling in the enterohepatic circulation.

5.3. Preclinical safety data

In the reproductive studies in rats (2, 8 or 32 mg/kg/day; 2-generation), no adverse effects were noted on gonadal function, fertility, gestation or neonatal viability, although the average weight in the high dose group was slightly reduced.

In dogs, testicular atrophy was noted after treatment with isotretinoin for approximately 30 weeks at dosages of 60 or 20 mg/kg/day. In general, there was microscopic evidence for appreciable depression of spermatogenesis but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen.

Carcinogenicity

In Fischer 344 rats given isotretinoin at dosages of 32 or 8 mg/kg/day for greater than 18 months, there was dose-related increased incidence of pheochromocytoma. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage. There is doubt as to the validity of this animal model as a predictor of tumorigenicity in man, as the Fischer rat is genetically predisposed to the Multiple Endocrine Neoplasia Syndrome which includes spontaneous occurrence of pheochromocytoma. In these studies, there was also a

dose-related decrease in the incidence of liver adenomata, liver angiomas and leukemia.

Teratogenicity

Isotretinoin is teratogenic in rats and rabbits although sensitivity differs. In the rat, doses up to 50 mg/kg/day were not teratogenic but 150 mg/kg/day was teratogenic. At lower doses in the rat perinatal and post-natal studies (5, 15 and 32 mg/kg/day) increased pup mortality was noted in all treatment groups. This was attributed to a dose-related reduction in maternal food intake. Body weight development of pups was significantly impaired in the high dose groups.

In the rabbit, a dose of 10 mg/kg/day caused abortions in 9 out of 13 animals and teratogenicity and embryotoxicity were observed in the remaining 4 litters.

Genotoxicity

Isotretinoin was negative in tests for gene mutation (histidine reversion in *S. typhimurium*), chromosomal damage *in vitro* (Chinese hamster lung cell and *S. cerevisiae* D7 assays) and *in vivo* (Mouse micronucleus test), and unscheduled DNA synthesis *in vitro* (rat hepatocytes).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

ORATANE 5 mg soft gelatin capsules contains the following excipients:

Butylated hydroxyanisole, disodium edetate, dl-Alpha tocopherol, gelatin, glycerol, hydrogenated vegetable oil, purified water, sorbitol, soya oil, titanium dioxide, and yellow beeswax.

ORATANE 10 mg soft gelatin capsule contains the following excipients:

Butylated hydroxyanisole, disodium edetate dihydrate, dl-Alpha tocopherol, gelatin, glycerol, hydrogenated vegetable oil, iron oxide black, ponceau 4R, purified water, sorbitol, soya oil, titanium dioxide, and yellow beeswax.

ORATANE 20 mg soft gelatin capsule contains the following excipients:

Butylated hydroxyanisole, disodium edetate dihydrate, dl-Alpha tocopherol, gelatin, glycerol, hydrogenated vegetable oil, indigo carmine, ponceau 4R, purified water, sorbitol, soya oil, titanium dioxide, and yellow beeswax.

ORATANE 30 mg soft gelatin capsule contains the following excipients:

Butylated hydroxyanisole, disodium edetate dihydrate, dl-Alpha tocopherol, gelatin, glycerol, iron oxide red, sorbitol, hydrogenated soya bean oil, soya oil, titanium dioxide, and yellow beeswax.

ORATANE 40 mg soft gelatin capsule contains the following excipients:

Butylated hydroxyanisole, disodium edetate dihydrate, all-rac-alpha-tocopherol, gelatin, glycerol, purified water, sorbitol, hydrogenated soya bean oil, soya oil, sunset yellow FCF, titanium dioxide, and yellow beeswax.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

ORATANE 5 mg, 10 mg, 20 mg, and 40 mg soft gelatin capsule

36 months from date of manufacture.

ORATANE 30 mg soft gelatin capsule

24 months from date of manufacture.

6.4. Special precautions for storage

ORATANE 5 mg, 10 mg, 30 mg, and 40 mg soft gelatin capsule

Store at or below 25°C and protect from light.

ORATANE 20 mg soft gelatin capsule

Store at or below 30°C and protect from light.

6.5. Nature and contents of container

ORATANE 5 mg soft gelatin capsules: PVC/PVDC-Aluminium blister packs containing 60 capsules.

ORATANE 10 mg soft gelatin capsules: PVC/PVDC-Aluminium blister packs containing 15 capsules as a starter pack, 60, 120 or 180 capsules.

ORATANE 20 mg soft gelatin capsules: PVC/PVDC-Aluminium blister packs containing 15 capsules as a starter pack, 60, 90, 120 or 180 capsules.

ORATANE 30 mg soft gelatin capsules: PVC/PVDC-Aluminium blister packs containing 60 or 120 capsules.

ORATANE 40 mg soft gelatin capsules: PVC/PVDC-Aluminium blister packs containing 30 capsules.

Not all strengths or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027

Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

ORATANE 5 mg soft gelatin capsules: 06 August 2009
ORATANE 10 mg soft gelatin capsules: 24 May 2001
ORATANE 20 mg soft gelatin capsules: 20 May 1999
ORATANE 30 mg soft gelatin capsules: 26 July 2012
ORATANE 40 mg soft gelatin capsules: 13 July 2006

10. DATE OF REVISION OF THE TEXT

29 October 2019.

Summary table of changes

Section Changed	Summary of new information
4.4	Minor editorial change.