SUMMARY OF PRODUCT CHARACTERISTICS

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 lengthand 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 inlength and 8 mm in diameter.

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

ORATANE 40 mg capsules: Soft gelatin oval opaque light orange capsules, approximately 13 mmlength 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 spreadover 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 inparticularly severe cases, the daily dosage may be increased to 1 mg/kg provided the medicine iswell 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, *see 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, *see Section 4.3.*

Paediatric population

Long term use in children under 13 years should be avoided because of a risk of premature epiphyseal closure, *see Section 4.8.*

Method of Administration

The daily dose is taken with meals.

4.3 Contraindications

Isotretinoin is contraindicated in women who are pregnant, *see 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 dysmorphia, 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.

Liver function

Liver function should be checked before and one month after the start of treatment and subsequently at three-monthly intervals.

Lipid metabolism and high-risk patients

Serum lipids (fasting value) should also be checked (before and one month after the start of therapy, and also at the end of the three-to-four-month treatment period). In high risk patients (with diabetes, obesity, alcoholism or disturbances of the lipid metabolism) undergoing treatment with isotretinoin, more frequent checks may be necessary. Isotretinoin should not be used together with any medicine known to enhance liver metabolism or interfere with enterohepatic circulation.

The serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment. The changes in serum lipids may also resolve in response to dietary measures.

It is recommended that clinically significant serum triglyceride elevations be controlled, since levels in excess of 800 mg/dL are sometimes associated with acute pancreatitis, which is known to be potentially fatal. Hence, isotretinoin should be discontinued if uncontrolled hypertriglyceridaemia or symptoms of pancreatitis occur.

In known or suspected diabetic patients, frequent determination of blood glucose levels is recommended. Although no causal relationship has been established, elevated fasting blood sugars have been reported and new cases of diabetes have been diagnosed during isotretinoin therapy.

Eye disorders

Patients, particularly those with dry eyes, should be monitored for the development of keratitis.

Decreased night vision has occurred during isotretinoin therapy and in rare instances has persisted 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.

Psychiatric disorders

Depression, *see Section 4.8,* psychotic symptoms and rarely suicide attempts and suicide have been reported in patients treated with isotretinoin. 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.

Benign intracranial hypertension

Rare cases of benign intracranial hypertension have been reported after isotretinoin and after tetracyclines, *See Section 4.8*. Supplementary treatment with tetracyclines is, therefore, contraindicated.

Musculo-skeletal and connective tissue disorders

Myalgia and arthralgia may occur and may be associated with reduced tolerance to vigorous exercise, *see Section 4.8*. Isolated instances of raised serum CPK values have been reported in patients receiving isotretinoin, particularly those undertaking vigorous physical activity.

Hyperostosis has been seen in some patients suffering from keratinising dermatoses on treatment with higher doses (> 2 mg/kg) and long-term administration (> 1 year).

Blood donation

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

Skin and subcutaneous tissues disorder

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

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.

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, *see Section 4.3 and 4.8*.

As tetracyclines can also cause 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 begiven, as required.

4.6 Fertility, pregnancy and lactation<u>**Pregnancy**</u>

Pregnancy (Category X)

Isotretinoin is highly teratogenic and must not be given to women who are pregnant, *see 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 ORATANE in any amount even for short periods. Potentially all exposed foetuses can be affected.

<u>Breast-feeding</u>

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.

<u>Fertility</u>

No data available.

4.7 Effects on ability to drive and use machines

Changes in vision, including decreased night vision, have been reported during isotretinoin therapy, see *Section 4.4 and 4.8*. Patients should be warned about the potential changes in vision, and advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known.

4.8 Undesirable effects

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

<u>Hypervitaminosis A</u>

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

Eye disorders Dryness of the eyes can cause conjunctivitis and reversible corneal opacities.

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

Skin and subcutaneous tissues disorders Exanthema, pruritus, dermatitis facialis, sweating, pyogenic granuloma, paronychia, nail dystrophy and increased formation of granulation tissue may occur. Rare cases of persistent hair thinning have been reported. Reversible alopecia has

been observed. Hirsutism, acne fulminans and hyperpigmentation (facial) have been reported rarely. Rarely, patients may experience photosensitivity reactions.
Musculo-skeletal and connective tissue disorders Bone changes and hyperostosis have occurred in children (including premature epiphyseal closure) and adults treated over long periods with high doses of isotretinoin generally for indications other than cystic acne. In one patient, spinal hyperostoses and calcification of the spinal ligaments with subsequent compression of the spinal cord were observed following long-term treatment over several years with another retinoid, etretinate. Isotretinoin is not intended for long-term therapeutic use, and the possibility of this adverse effect occurring if it is used improperly for long-term treatment should be borne in mind.

Minimal hyperostosis has been observed in cystic acne patients treated with a single course of isotretinoin. Due to the possible occurrence of these bone changes, a careful evaluation of the risk/benefit ratio should be carried out in every patient and isotretinoin administration shouldbe restricted to severe cases.

Vascular disorders

There have been cases of allergic vasculitis including Wegener's granulomatosis,

Blood and lymphatic system disorders

There have been cases of reduction in white and red blood cell counts including anaemia and neutropenia, increases and decreases in platelet count, elevated sedimentation rate.

Respiratory, thoracic and mediastinal disorders

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

Psychiatric disorders and Nervous system disorders

Behavioural disorders, depression (*see Section 4.4*), headache, increased intracranial pressure (pseudotumor cerebri) and seizures.

Investigations

Transitory and reversible increases in transaminases as well as some cases of hepatitis related to isotretinoin have been observed. In many such cases the changes have been within the normal range and values have returned to baseline levels during treatment. In other cases, however, it has been necessary to reduce the dosage or discontinue treatment with isotretinoin

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

Reproductive system and breast disorders

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

Other effects

Isolated cases of benign intracranial hypertension and visual disturbances, and occasionally nausea and headache have been observed.

Pancreatitis and haematuria/proteinurea occur rarely.

Impaired hearing in certain frequencies and local or systemic infections due to Gram-positive microorganisms (Staphylococcus aureus) have been reported.

Muscle and joint pain and, more rarely, overdosage, inflammatory bowel disease (eg. Colitis, ileitis haemorrhage), and hyperuricaemia have been reported.

Lymphadenopathy has occasionally been noted.

Paediatric population

Bone changes and hyperostosis have occurred in children (including premature epiphyseal closure)

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).

5.1 Pharmacological Properties

5.2 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 provedinsufficiently 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.

5.3 Pharmacokinetic properties

Absorption

Time-related blood concentrations can be predicted on the basis of linear pharmacokinetics. Peak plasma concentrations (C_{max}) of approximately 200-300 ng/ml have been achieved in healthy volunteers three to four hours (t_{max}) after administration of 40 mg isotretinoin.

Taking isotretinoin with food increases bioavailability up to twofold relative to fasting conditions, probably as a result of easier absorption of this highly lipophilic medication. Furthermore, there is an overall decrease in fluctuations in systemic availability when isotretinoin is ingested with food.

Distribution

Isotretinoin is extensively bound to plasma proteins (99.9 %) with the result that the free active fraction of the substance is less than 0.1 % of the total over a wide range of therapeutic concentrations. Albumin appears to be the major binding protein.

The volume of distribution of isotretinoin is not known in humans since it is not available as an intravenous preparation.

Biotransformation

Three major metabolites have been identified in plasma: 4-oxo-isotretinoin, tretinoin (all-trans retinoic acid), and 4-oxo-tretinoin. The major blood metabolite of isotretinoin is 4-oxo-isotretinoin, which is rapidly formed following oral administration achieving peak concentrationsof 100 - 140 ng/ml at about two hours after administration of 40 mg isotretinoin. Other minor metabolites have been detected but are not completely identified, which also includes glucuronide conjugates.

Isotretinoin metabolites have shown biological activity in several *in vitro* tests. Thus the observed clinical profile in patients could be the result of the pharmacological activity of isotretinoin and its metabolites.

Since isotretinoin and tretinoin (all-trans retinoic acid) are reversibly metabolised (= interconverted), the metabolism of tretinoin is linked with that of isotretinoin. It has been estimated that 20-30% of an isotretinoin dose is metabolised by isomerization.

Isotretinoin also isomerises in vivo via an alternative metabolic pathway to tretinoin (all-trans retinoic acid). Glucuronidation of the metabolites has not been conclusively demonstrated in humans but is strongly suggested by animal studies. Investigations in humans and dogs point toan enterohepatic recirculation of isotretinoin, which would contribute to the observed inter-individual variability in plasma concentrations. In *vitro* metabolism studies have demonstrated that several CYP enzymes are involved in the metabolism of isotretinoin to 4-oxo-isotretinoin

and tretinoin. No single isoform appears to have a predominant role. CYP2C8, CYP2C9, CYP2B6, and possibly CYP3A4 appear to have the greatest contributions in the metabolism of isotretinoin to 4-oxo-isotretinoin. CYP2C9, CYP2B6, and possibly CYP2C8, CYP3A4, CYP2A6, and CYP2E1 contribute to the metabolism of isotretinoin. CYP26 is also known to metabolize retinoids

Elimination

Isotretinoin appears to be eliminated almost exclusively by hepatic metabolism and biliary excretion.

Following oral administration of isotretinoin, the elimination half-life of unchanged substance has ranged from 7 to 39 hours (mean approximately 20 hours) in both healthy volunteers and patients with cystic acne.

The mean elimination half-life of the 4-oxo metabolite in patients with cystic acne is slightly longer (25 hours, range: 17-50 hours) than that of the parent substance.

Isotretinoin is a physiological retinoid and endogenous retinoid concentrations are reached within approximately two weeks following the end of isotretinoin therapy.

Special populations

Hepatic impairment

Since isotretinoin is contraindicated in patient's hepatic impairment *(see Section 4.3)*, there is no information on the pharmacokinetics of the substance in this population.

5.3 Preclinical safety data

Not applicable.

5. 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 120capsules.

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.

6. Marketing Authorization Holder

Douglas Pharmaceuticals LtdP O Box 45 027
Auckland 0651New Zealand
Phone: (09) 835 0660

7. Marketing Authorization Number

TAN 21 HM 0038

8. Date of First Approval

24/12/2020

9. Date of Revision of Text

March 2021