Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oratan 10 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 10 mg isotretinoin.

Excipients: Each soft capsule contains 132.80 mg soya bean oil, 5.31 mg sorbitol (E420) and 0.0026 mg Ponceau 4R red (E124).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft

Light violet coloured oblong soft gelatin capsules, containing a yellow/orange opaque viscous liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Severe forms of acne (such as nodular or conglobate acne at risk of permanent scarring) resistant to adequate course of standard therapy with systemic antibacterials and topical therapy.

4.2 Posology and method of administration

Isotretinoin should only be prescribed by or under the supervision of physicians 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 capsules should be taken with food once or twice daily.

Adults including adolescents and the elderly:
Isotretinoin therapy should be started at a dose of 0.5 mg/kg daily. The therapeutic response to isotretinoin and some of the adverse effects are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy. For most patients, the dose ranges from 0.5 – 1.0 mg/kg per day.

Long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose. It has been shown that no substantial additional benefit is to be expected beyond a cumulative treatment dose of 120-150 mg/kg. The duration of treatment will depend on the individual daily dose. A treatment course of 16-24 weeks is normally sufficient to achieve remission.
In the majority of patients, complete clearing of the acne is obtained with a single treatment course. In the event of a definite relapse a further course of isotretinoin therapy may be considered using the same daily dose and cumulative treatment dose.

As further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, a further course of treatment should not be considered until at least this period has elapsed.

Patients with severe renal insufficiency
In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 10 mg/day). The dose should then be increased up to 1 mg/kg/day or until the patient is receiving the maximum tolerated dose (see section 4.4 "Special warnings and precautions for use").

Children
This product is not indicated for the treatment of prepubertal acne and is not recommended in patients less than 12 years of age.

Patients with intolerance
In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequences of longer therapy duration and a higher risk of relapse. In order to achieve the maximum possible efficacy in these patients the dose should normally be continued at the highest tolerated dose.

4.3 Contraindications

Isotretinoin is contraindicated in women who are pregnant or breastfeeding.
(See section 4.6 “Pregnancy and lactation”).

Isotretinoin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.4 “Special warnings and precautions for use”).

Isotretinoin is also contraindicated in patients
- With hepatic insufficiency
- With excessively elevated blood lipid values
- With hypervitaminosis A
- With hypersensitivity to isotretinoin, soya oil or to any of the excipients
- Receiving concomitant treatment: with tetracyclines (see section 4.5 “Interaction with other medicinal products and other forms of interactions”).

4.4 Special warnings and precautions for use

Pregnancy Prevention Programme

This medicinal product is TERATOGENIC.

Isotretinoin is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme arc 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 (see section 4.1 “Therapeutic indications”).
- 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 amenorrhea 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.

Contraception
Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception.

As a minimum requirement, female patients at potential risk of pregnancy must use at least one effective method of contraception. Preferably the patient should use two complementary forms of contraception including a barrier method. Contraception should be continued for at least 1 month after stopping treatment with isotretinoin, even in patients with amenorrhoea.

Pregnancy testing
According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25mlU/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 isotretinoin.

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 of amenorrhea). 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 Isotretinoin 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 isotretinoin should occur on the same day. Dispensing of isotretinoin should occur within a maximum of 7 days of the prescription.

Male patients
There is no evidence to suggest that the fertility or offspring of male patients will be affected by them taking isotretinoin. However, male patients should be reminded that they must not share their medication with anyone, particularly not females.

Additional precautions
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy and for 1 month following discontinuation of isotretinoin because of the potential risk to the foetus of a pregnant transfusion recipient.

Educational material
In order to assist prescribers, pharmacists and patients in avoiding foetal exposure to isotretinoin the Marketing Authorisation Holder will provide educational material to reinforce the warnings about the teratogenicity of isotretinoin, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

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 physician to all patients, both male and female.

Psychiatric disorders
Depression, psychotic symptoms and, rarely, suicide attempts and suicide have been reported in patients treated with isotretinoin (see section 4.8 “Undesirable effects”). 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 isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

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 SFP 15 should be used.

Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on isotretinoin 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 isotretinoin for at least a period of 6 months after treatment because of the risk of epidermal stripping.

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents 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 isotretinoin is likely to cause dryness of the skin and lips.

Eye disorders
Dry eyes, corneal opacities, 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. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.

Decreased night vision has also been reported and the onset in some patients was sudden (see section 4.7 “Effects on ability to drive and to use machines”). Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion. Withdrawal of isotretinoin may be necessary.

Musculo-skeletal and connective disorders
Myalgia, arthralgia and increased serum creatine phosphokinase values have been reported in patients receiving isotretinoin, particularly in those undertaking vigorous physical activity (see section 4.8 “Undesirable effects”).

Bone changes including premature epiphyseal closure, hyperostosis, 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.

Benign intracranial hypertension
Cases of benign intracranial hypertension have been reported, some of which involved concomitant use of tetracyclines (see sections 4.3 “Contraindications” and 4.5 “Interactions with other medicinal products and other forms of interaction”). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema. Patients who develop benign intracranial hypertension should discontinue isotretinoin immediately.

Hepatobiliary disorders
Liver enzymes should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Transient and reversible increases in liver transaminases have been reported. In many cases these changes have been within the normal range and values have returned to baseline levels during treatment. However, in the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.

Renal insufficiency
Renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Therefore, isotretinoin 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 (sec section 4.2 “Posology and Method of Administration”).

Lipid Metabolism
Serum lipids (fasting values) should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Elevated serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment and may also respond to dietary measures.

Isotretinoin has been associated with an increase in plasma triglyceride levels. Isotretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur (see section 4.8 “Undesirable effects”). Levels in excess of 800mg/dL or 9mmol/L are sometimes associated with acute pancreatitis, which may be fatal.

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 (hemorrhagic) diarrhoea should discontinue isotretinoin immediately.

Allergic reactions
Anaphylactic reactions have been rarely 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 isotretinoin, 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 isotretinoin therapy.

Information on certain excipients:
Soya oil (see 4.3 “contraindications”) and Ponceau 4R red (E124) may cause allergic reactions.

The capsules contain sorbitol (E 420). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should not take vitamin A as concurrent medication due to the risk of developing hypervitaminosis A.

Cases of benign intracranial hypertension (pseudotumor cerebri) have been reported with concomitant use of isotretinoin and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see section 4.3 “Contraindications” and section 4.4 “Special warnings and Precautions for use”).

4.6 Pregnancy and lactation

Pregnancy is an absolute contraindication to treatment with isotretinoin (see section 4.3 “Contraindications”). If pregnancy does occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe and serious malformations of the foetus

The foetal malformations associated with exposure to isotretinoin include central nervous system abnormalities (hydrocephalus. cerebellar malformation/abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (micophthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallut, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities, There is also an increased incidence of spontaneous abortion.

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

Lactation
Isotretinoin is highly lipophilic, therefore the passage of isotretinoin into human milk is very likely. Due to the potential for adverse effects in the mother and exposed child the use of isotretinoin is contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines

A number of cases of decreased night vision have occurred during isotretinoin therapy and in rare instances have persisted after therapy (see section 4.4 “Special warnings and precautions for use” and section 4.8 “Undesirable effects”). Because the onset in some patients was sudden patients should be advised of this potential problem and warned to be cautious when driving or operating machines.

4.8 Undesirable effects

The following symptoms are the most commonly reported undesirable effects with Isotretinoin: dryness of the mucosa e.g. of the lips, cheilitis, the nasal mucosa, epistaxis, and the eyes, conjunctivitis, dryness of the skin. Some of the side effects associated with the use of isotretinoin are dose-related. The side effects are generally reversible after altering the dose or discontinuation of treatment; however some may persist after treatment has stopped.

Infections:
Very rare (≤1/10 000), including isolated cases: Gram positive (mucocutaneous) bacterial infection.

Blood and lymphatic system disorders
Very common (≥1/10): Anaemia, Red blood cell sedimentation rate increased, Thrombocytopenia, Thrombocytosis.
Common (≥1/100, <1/10): Neutropenia.
Very rare (≤1/10 000), including isolated cases: Lymphadenopathy.

Immune system disorders:
Rare (≥1/10 000, <1/1000): Allergic skin reaction, Anaphylactic reactions, Hypersensitivity.

Metabolism and nutrition disorders
Very rare (≤1/10 000), including isolated cases: Diabetes mellitus; Hyperuricaemia.

Psychiatric disorders
Rare (≥1/10 000, <1/1000): Depression.
Very rare (≤1/10 000), including isolated cases: Abnormal behavior; Psychotic disorder; Suicide attempt; Suicide.

Nervous system disorders
Common (≥1/100, <1/10): Headache.
Very rare (≤1/10 000), including isolated cases: Benign intracranial hypertension; Convulsions; Drowsiness.

Eye disorders
Very common (≥1/10): Blepharitis; Conjunctivitis; Dry eye; Eye irritation.
Very rare (≤1/10 000), including isolated cases: Blurred vision; Cataract; Colour blindness (colour vision deficiencies); Contact lens intolerance; Corneal opacity; Decreased night vision; Keratitis; Papilloedema (as sign of benign intracranial hypertension); Photophobia.

Ear and labyrinth disorders
Very rare (≤1/10 000), including isolated cases: Hearing impaired.

Vascular disorders
Very rare (≤1/10 000), including isolated cases: Vasculitis (for example Wegener's granulomatosis, allergic vasculitis).

Respiratory, thoracic and mediastinal disorders
Common (≥1/100, <1/10): Epistaxis; Nasal dryness; Nasopharyngitis.
Very rare (≤1/10 000), including isolated cases: Bronchospasm (particularly in patients with asthma); Hoarseness.

Gastrointestinal disorders
Very rare (≤1/10 000), including isolated cases: Colitis; Ileitis; Dry throat; Gastrointestinal haemorrhage; haemorrhagic diarrhea and inflammatory bowel disease; Nausea; Pancreatitis (see section 4.4 "Special warnings and precautions for use").

Hepatobiliary disorders
Very common (≥1/10): Transaminase increased (see section 4.4 "Special warnings and precautions for use").
Very rare (≤1/10 000), including isolated cases: Hepatitis.

Skin and subcutaneous tissue disorders
Very common (≥1/10): Cheilitis; Dermatitis; Dry skin; Localised exfoliation; Pruritus; Rash erythematous; Skin fragility (risk of frictional trauma).
Rare (≥1/10 000, <1/1000): Alopecia.
Very rare (≤1/10 000), including isolated cases: Acne fulminans; Acne aggravated (acne flare); Erythema (facial); Exanthema; Hair disorders, Hirsutism; Nail dystrophy, Paronychia, Phaotosensitivity reactions, Pyogenic granuloma; Skin hyperperpigmentation, Sweating increased.

Musculo-skeletal and connective tissue disorders
Very common (≥1/10): Arthralgia; Myalgia, Back pain (particularly adolescent patients).
Very rare (≤1/10 000), including isolated cases: Arthritis; Calcinosis (calcification of ligaments and tendons); Epiphyses premature fusion; Exostosis; (hyperostosis); Reduced bone density, Tendonitis.

Renal and urinary disorders
Very rare (≤1/10 000), including isolated cases: Glomerulonephritis.

General disorders and administration site conditions
Very rare (≤1/10 000), including isolated cases: Granulation tissue (increased formation of) Malaise.

Investigations
Very common (≥1/10): Blood triglycerides increased; High density lipoprotein decreased.
Common (≥1/100, <1/10): Blood cholesterol increased; Blood glucose increased; Haematuria; Proteinuria.
Very rare (≤1/10 000), including isolated cases: Blood creatine phosphokinase increased.

[The incidence of the adverse events was calculated from pooled clinical trial data involving 824 patients and from post-marketing data.]

4.9 Overdose

Isotretinoin is a derivative of vitamin A. Although the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in cases of occidental overdose. Manifestations of acute Vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with Isotretinoin would probably be similar. These symptoms would be expected to be reversible and to subside without the need for treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-acne preparations for systemic use
ATC code: DI0BA01

Mechanism of action
Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin). The exact 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 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.

Efficacy
Hypercornification of the epithelial lining of the pilosebaceous unit leads to shedding of corneocytes into the duct and blockage by keratin and excess sebum. This is followed by formation of a comedone and, eventually inflammatory lesions. Isotretinoin inhibits proliferation of sebocytes and appears to act in acne by re-setting the orderly program of differentiation. Sebum is a major substrate for the growth of Propionibacterium acnes so that reduced sebum production inhibits bacterial colonisation of the duct.

5.2 Pharmacokinetic properties

Absorption:
The absorption of isotretinoin from the gastro-intestinal tract is variable and dose-linear over the therapeutic range. The absolute bioavailability of isotretinoin has not been determined, since the compound is not available as an intravenous preparation for human use, but extrapolation from dog studies would suggest a fairly low and variable systemic bioavailability. When, isotretinoin is taken with food, the bioavailability is doubled relative to fasting conditions.

Distribution:
Isotretinoin is extensively bound to plasma proteins, mainly albumin (99.9%). The volume of distribution of isotretinoin in man has not been determined since isotretinoin is not available as an intravenous preparation for human use. In humans little information is available on the distribution of isotretinoin into tissue. Concentrations of isotretinoin in the epidermis are only half of those in serum. Plasma concentrations of isotretinoin are about ***1.7*** times those of whole blood due to poor penetration of isotretinoin into red blood cells.

Metabolism:
After oral administration of isotretinoin, three major metabolites have been identified in plasma: 4-oxo-isotretinoin, tretinoin, (all-trans retinoic acid) and 4-oxo-tretinoin. These metabolites have shown biological activity in several in vitro tests. 4-oxo-isotretinoin has been shown in a clinical study to be a significant contributor to the activity of isotretinoin (reduction in sebum excretion rate despite no effect on plasma levels of isotretinoin and tretinoin). Other minor metabolites include glucuronide conjugates. 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 and tretinoin (all-trans retinoic acid) are reversibly metabolised (interconverted), and the metabolism of tretinoin is therefore linked with that of isotretinoin. 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 man. 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. Isotretinoin and its metabolites do not significantly affect CYP activity.

Elimination:
After oral administration of radiolabelled isotretinoin approximately equal fractions of the dose were recovered in urine and faeces. Following oral administration of isotretinoin, the terminal elimination half-life of unchanged drug 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 isotretinoin 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. Renal failure does not significantly reduce the plasma clearance of isotretinoin or 4-oxo-isotretinoin.

5.3 Preclinical safety data

Acute toxicity
The acute oral toxicity of isotretinoin was determined in various animal species. LD50 is approximately 2000 mg/kg in rabbits, approximately 3000 mg/k in mice, and over 4000 mg/kg in rats.

Chronic toxicity
A long-term study in rats over 2 years (isotretinoin dosage 2, 8 and 32 mg/kg/d) produced evidence of partial hair loss and elevated plasma triglycerides in the higher dose groups. The side effect spectrum of isotretinoin in the rodent thus closely resembles that of vitamin A, but does not include the massive tissue and organ calcifications observed with vitamin A in the rat. The liver cell changes observed with vitamin A did not occur with isotretinoin.
All observed side effects of hypervitaminosis A syndrome were spontaneously reversible after withdrawal of isotretinoin, even experimental animals in a poor general state had largely recovered within 1-2 weeks.

Teratogenicity
Like other vitamin A derivatives, isotretinoin has been shown in animal experiments to be teratogenetic and embryotoxic.

Due to the teratogenetic potential of isotretinoin there are therapeutic consequences for the administration to women of a childbearing age (see section 4.3 “Contraindications”, section 4.4 “Special warnings and precautions for use” and section 4.6 “Pregnancy and lactation”).

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.

Mutagenicity
Isotretinoin has not been shown to be mutagenic nor carcinogenic in in-vitro or in-vivo animal tests respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil, refined
All-rac-α-tocopherol
Disodium edetate
Butyl hydroxyanisole
Hydrogenated vegetable oil
Soya-bean oil, partly hydrogenated
Beeswax yellow

Capsule shell:
Gelatin,
Glycerol
Sorbitol (E420)
Ponceau 4R (E 124)
Black iron oxide (E 172)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

PVC/PVDC/aluminium foil blisters

Pack sizes: 5, 10, 15, 20, 28, 30, 50, 56, 60 or 100 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
County Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 0126/130/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 January 2004
Date of last renewal: 21 March 2007

10 DATE OF REVISION OF THE TEXT

September 2008