SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

/.../ 10 mg soft capsules
/.../ 20 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10 mg isotretinoin.

Excipients with known effect
Each capsule contains 140.5 mg soya-bean oil, 0.0026 mg Cochineal red A (E124) and 5.3 mg sorbitol (on dried weight basis)
For the full list of excipients, see section 6.1.

Each capsule contains 20 mg isotretinoin.

Excipients with known effect
Each capsule contains 281 mg soya-bean oil, 0.336 mg Cochineal red A (E124) and 17.0 mg sorbitol (on dried weight basis)
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, soft.

/.../ 10 mg: Light violet coloured, oval, soft gelatine capsules, containing a yellow/orange opaque viscous liquid, 10 mm x 7 mm in size.
/.../ 20 mg: Maroon coloured, oval, soft gelatine capsules, containing a yellow/orange opaque viscous liquid, 13 mm x 8 mm in size.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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.

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. 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).

Paediatric population
Isotretinoin 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 a 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.

Method of administration
The capsules should be taken with food once or twice daily.

4.3 Contraindications

Isotretinoin is contraindicated in women who are pregnant or breastfeeding (see section 4.6).

Isotretinoin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.4).

Isotretinoin is also contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
/.../ contains refined soya-bean oil and partially hydrogenated soya-bean oil. Therefore, /.../ is contraindicated in patients allergic to peanut or soya.

Isotretinoin is also contraindicated in patients:
- With hepatic insufficiency
- With excessively elevated blood lipid values
- With hypervitaminosis A
- Receiving concomitant treatment with tetracyclines (see section 4.5)

4.4 Special warnings and precautions for use

Teratogenic effects
/.../ is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects.
/.../ is strictly contraindicated in:
- Pregnant women

- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met

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 are met:

- She has severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic anti-bacterials and topical therapy (see section 4.1 „Therapeutic indications“).
- The potential for pregnancy must be assessed for all female patients.
- 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 entire duration of treatment and for 1 month after the end of treatment. At least one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception should be used.
- Individual circumstances should be evaluated in each case, when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.
- Even if she has amenorrhea she must follow all the advice on effective contraception.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy or if she might be pregnant.
- She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and 1 month after stopping 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 understands that she must consistently and correctly use one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception, 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 1 month after the end of treatment. The dates and results of pregnancy tests should be documented.

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.

If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the fetus. This risk persists until the product has been completely eliminated, which is within one month following the end of treatment.

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. If the prescribing physician is not in a position to provide such information the patient should be referred to the relevant healthcare professional.

As a minimum requirement, female patients of childbearing potential must use at least one highly effective method of contraception (i.e. a user-independent form), or two complementary user-dependent forms of contraception. Contraception should be used for at least 1 month prior to starting treatment, throughout treatment and continue for at least 1 month after stopping treatment with isotretinoin, even in patients with amenorrhea.

Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

Pregnancy testing
According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL are recommended to be performed, as follows.

Prior to starting therapy
At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a medically supervised pregnancy test. 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 regular intervals, ideally monthly. 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, recent menstrual history (abnormal menses, missed periods or amenorrhea) and method of contraception. 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
1 month after stopping treatment, women should undergo a final pregnancy test.

Prescribing and dispensing restrictions
For women of childbearing potential, the prescription duration of /.../ should ideally be limited to 30 days in order to support regular follow up, including pregnancy testing and monitoring. Ideally, pregnancy testing, issuing a prescription and dispensing of /.../ should occur on the same day.

This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patient is not pregnant before receiving the next cycle of medication.

Male patients
The available data suggest that the level of maternal exposure from the semen of the patients receiving /.../, is not of a sufficient magnitude to be associated with the teratogenic effects of /.../.

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 fetal 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, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin (see section 4.8). Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Awareness by family or friends may be useful to detect mental health deterioration.

Skin and subcutaneous tissues disorders
Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually within 7 - 10 days, and usually does not require dose adjustment.

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

Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on 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 (see section 4.5).

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 (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) associated with isotretinoin use. As these events may be difficult to distinguish from other skin reactions that may occur (see section 4.8), patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. If a severe skin reaction is suspected, isotretinoin treatment should be discontinued.

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.

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). Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion. Withdrawal of isotretinoin may be necessary.

Musculoskeletal and connective tissue 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).

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 and 4.5). 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 (see section 4.2).

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). Levels in excess of 800 mg/dL or 9 mmol/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.

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 for blood glucose may be necessary. Elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during isotretinoin therapy.

/…/ contains sorbitol
This medicine contains 5.3 mg sorbitol (on dried weight basis) in each 10 mg capsule and 17.0 mg sorbitol (on dried weight basis) in each 20 mg capsule.

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 sections 4.3 and 4.4).

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy is an ABSOLUTE contraindication to treatment with isotretinoin (see section 4.3). 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 malformation 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 (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, 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.

Breastfeeding

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

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.

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 sections 4.4 and 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 machines.

Drowsiness, dizziness and visual disturbances have been reported very rarely. Patients should be warned that if they experience these effects, they should not drive, operate machinery or take part in any other activities where the symptoms could put either themselves or others at risk

4.8 Undesirable effects

Summary of safety profile

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. 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.

Tabulated list of adverse reactions

The incidence of the adverse reactions calculated from pooled clinical trial data involving 824 patients and from post-marketing data are presented in the table below. The adverse reactions are listed below by MedDRA system organ class (SOC) and categories of frequency. Frequency categories are defined as: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Infections and infestations	
Very rare	Gram positive (mucocutaneous) bacterial infection
Blood and lymphatic system disorders	
Very common	Anemia, red blood cell sedimentation rate increased, thrombocytopenia, thrombocytosis
Common	Neutropenia
Very rare	Lymphadenopathy
Immune system disorders	
Rare	Allergic skin reaction, anaphylactic reactions, hypersensitivity
Metabolism and nutrition disorders	
Very rare	Diabetes mellitus, hyperuricaemia
Psychiatric disorders	
Rare	Depression, depression aggravated, aggressive tendencies, anxiety, mood alterations.
Very rare	Suicide, suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour
Nervous system disorders	
Common	Headache
Very rare	Benign intracranial hypertension, convulsions, drowsiness, dizziness
Eye disorders	
Very common	Blepharitis, conjunctivitis, dry eye, eye irritation
Very rare	Blurred vision, cataract, colour blindness (colour vision deficiencies), contact lens intolerance, corneal opacity, decreased night vision, keratitis, papilloedema (as sign of benign intracranial hypertension), photophobia, visual disturbances
Ear and labyrinth disorders	
Very rare	Hearing impaired
Vascular disorders	
Very rare	Vasculitis (for example Wegener's granulomatosis, allergic vasculitis)
Respiratory, thoracic and mediastinal disorders	
Common	Epistaxis, nasal dryness, nasopharyngitis
Very rare	Bronchospasm (particularly in patients with asthma), hoarseness
Gastrointestinal disorders	
Very rare	Colitis, ileitis, dry throat, gastrointestinal haemorrhage, haemorrhagic diarrhoea and inflammatory bowel disease, nausea, pancreatitis (see section 4.4)
Hepatobiliary disorders	
Very common	Transaminase increased (see section 4.4)

Very rare	Hepatitis
Skin and subcutaneous tissue disorders	
Very common	Cheilitis, dermatitis, dry skin, localised exfoliation, pruritus, rash erythematous, skin fragility (risk of frictional trauma)
Rare	Alopecia
Very rare	Acne fulminans, acne aggravated (acne flare), erythema (facial), exanthema, hair disorders, hirsutism, nail dystrophy, paronychia, photosensitivity reaction, pyogenic granuloma, skin hyperpigmentation, sweating increased
Not known	Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis.
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, myalgia, back pain (particularly adolescent patients)
Very rare	Arthritis, calcinosis (calcification of ligaments and tendons), epiphyses premature fusion, exostosis, (hyperostosis), reduced bone density, tendonitis, rhabdomyolysis
Renal and urinary disorders	
Very rare	Glomerulonephritis
Reproductive system and breast disorders	
Not known	Sexual dysfunction including erectile dysfunction and decreased libido
General disorders and administration site conditions	
Very rare	Granulation tissue (increased formation of), malaise
Investigations	
Very common	Blood triglycerides increased, high density lipoprotein decreased
Common	Blood cholesterol increased, blood glucose increased, haematuria, proteinuria
Very rare	Blood creatine phosphokinase increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 accidental overdose. Symptoms 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: D10BA01

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.

Clinical efficacy and safety
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.

Biotransformation
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/kg 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.

All observed side effects of hypervitaminosis A syndrome were 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 teratogenic and embryotoxic.

Due to the teratogenic potential, the use for women of a childbearing age of isotretinoin is restricted (see sections 4.3, 4.4 and 4.6).

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-alpha-tocopherol (E307)
Disodium edetate
Butylhydroxyanisole (BHA E320)
Soya-bean oil (partly hydrogenated)
Hydrogenated vegetable oil
Beeswax yellow

Capsule shell
10 mg capsules:
Gelatin
Glycerol
Sorbitol
Purified water
Titanium dioxide (E 171)
Cochineal red A (E124)
Black iron oxide (E172)

20 mg capsules:
Gelatin
Glycerol
Sorbitol
Purified water
Titanium dioxide (E171)
Indigotine lacquer (E132)
Cochineal red A (E124)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC-aluminum foil blisters.

Pack sizes: 10, 20, 30, 60, 90, 100 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

<[To be completed nationally]>

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for blister

1. NAME OF THE MEDICINAL PRODUCT

/.../ 10 mg soft capsules
/.../ 20 mg soft capsules
isotretinoin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 10 mg isotretinoin.
Each capsule contains 20 mg isotretinoin.

3. LIST OF EXCIPIENTS

Contains colouring agent (E124), sorbitol and soya-bean oil. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 soft capsules
20 soft capsules
30 soft capsules
60 soft capsules
90 soft capsules
100 soft capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

WARNING

CAN SERIOUSLY HARM AN UNBORN BABY

Women must use effective contraception

Do not use if you are pregnant or think you may be pregnant

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the blister in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

/.../ 10 mg
/.../ 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

Blister

1. NAME OF THE MEDICINAL PRODUCT

/.../ 10 mg soft capsules
/.../ 20 mg soft capsules
isotretinoin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the user

/.../ 10 mg and 20 mg soft capsules
isotretinoin

WARNING

CAN SERIOUSLY HARM AN UNBORN BABY

Women must use effective contraception

Do not use if you are pregnant or you think you may be pregnant

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What /.../ is and what it is used for

/.../ contains the active substance isotretinoin which belongs to a group of drugs called retinoids which are structurally related to vitamin A. It reduces the activity of sebaceous glands which produce fat in the skin.

/.../ is a prescription drug and is indicated for the treatment of severe acne, e.g. nodular or conglobate acne or acne at risk of permanent scarring, which does not respond to standard therapy with systemic antibacterials and topical therapy.

It is recommended that the treatment is controlled or supervised by a specialist (e.g. dermatologist) with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.

2. What you need to know before you take /.../

Do not take /.../
- if you are pregnant or breast-feeding

- if there is any chance you could become pregnant, you must follow the precautions under ”Pregnancy Prevention Programme”, see section on ”Warnings and precautions”
- if you are allergic to isotretinoin, soya, peanut or any of the other ingredients of this medicine (listed in section 6)
- if your liver function is reduced
- if you have increased level of fat in your blood (e.g. high cholesterol or triglycerides)
- if you have very high levels of vitamin A in your body (hypervitaminosis A)
- at the same time as antibiotics containing tetracyclines (see ‘Other medicines and /…/’).

Warnings and precautions
Talk to your doctor or pharmacist before taking /…/.

Pregnancy Prevention Programme

Women who are pregnant must not take /.../
This medicine can seriously harm an unborn baby (the medicine is said to be ‘teratogenic’) – it can cause serious abnormalities of the unborn baby’s brain, face, ear, eye, heart and certain glands (thymus gland and parathyroid gland). It also makes a miscarriage more likely. This may happen even if /…/ is taken only for a short time during pregnancy.

- You must not take /.../ if you are pregnant or if you think you might be pregnant.
- You must not take /.../ if you are breastfeeding. The medicine is likely to pass into your milk and may harm your baby.
- You must not take /.../ if you could get pregnant during treatment.
- You must not get pregnant for one month after stopping this treatment because some medicine may still be left in your body.

Women who could get pregnant are prescribed /.../ under strict rules. This is because of the risk of serious harm to the unborn baby.
These are the rules:
- Your doctor must explain the risk of harm to the unborn baby - you must understand why you must not get pregnant and what you need to do to prevent getting pregnant.
- You must have talked about contraception (birth control) with your doctor. The doctor will give you information on how not to get pregnant. The doctor may send you to a specialist for contraception advice.
- Before you start treatment, your doctor will ask you to take a pregnancy test. The test must show that you are not pregnant when starting treatment with /.../.

Women must use effective contraception before, during and after taking /…/
- You must agree to use at least one very reliable method of contraception (for example an intra uterine device or contraceptive implant) or, two effective methods that work in different ways (for example a hormonal contraceptive pill and a condom). Discuss with your doctor which methods would be suitable for you.
- You must use contraception for a month before taking /…/, during treatment and for a month afterwards.
- You must use contraception even if you do not have periods or you are not sexually active (unless your doctor decides this is not necessary).

Women must agree to pregnancy testing before, during and after taking /…/
- You must agree to regular follow-up visits, ideally every month.
- You must agree to have regular pregnancy tests, ideally every month during treatment and, because some medicine may still be left in your body, 1 month after stopping /…/ (unless your doctor decides this is not necessary in your case).
- You must agree to extra pregnancy tests if your doctor asks you.
- You must not get pregnant during treatment or for a month afterwards because some medicine may still be left in your body.

- Your doctor will discuss all these points with you, using a checklist and will ask you (or a parent/guardian) to sign it. This form confirms that you have been told about the risks and that you will follow the rules above.

If you get pregnant while taking /…/, **stop taking the medicine straight away,** and contact your doctor. Your doctor may send you to a specialist for advice.

Also, if you become pregnant within one month after you stop taking /…/, you should contact your doctor. Your doctor may send you to a specialist for advice.

Advice for men
The levels of oral retinoid in the semen of men taking /…/ are too low to harm their partners' unborn baby. However, you must never share your medication with anyone.

Additional precautions

You should never give this medicinal product to another person. Please take any unused capsules to your pharmacist at the end of treatment.

You should not donate blood during treatment with this medicine and for 1 month after stopping /…/ because an unborn baby could be harmed if a pregnant patient receives your blood.

Special precautions for all patients
- Talk to your doctor before taking /…/ if you have ever had any kind of mental health problems. This includes depression, aggressive tendencies or mood changes. It also includes thoughts about hurting yourself or ending your life. This is because your mood may be affected while taking /…/.
- Your skin is likely to become dry. Use a skin moisturising ointment or cream and a lip balm during treatment. To prevent skin irritation you should avoid using exfoliating or anti-acne products not prescribed by the doctor.
- Avoid too much sun and do not use a sunlamp or sunbed. Your skin may become more sensitive to sunlight. Before you go out in the sun, use a sun- protection product with a high protection factor (SPF 15 or higher).
- Do not have any cosmetic skin treatments. /.../ may make your skin more fragile. Do not have any waxing (hair removal), dermabrasion or laser treatments (removing horny skin or scars) during treatment, or for at least 6 months after treatment. They could cause scarring, skin irritation, or rarely, changes in the colour of your skin.
- /…/ may cause dry eyes and visual difficulties. Dry eyes can be helped by application of a lubricating eye ointment or by tear replacement therapy. Intolerance to contact lenses may occur, which may necessitate the use of glasses during treatment. Decreased night vision can happen quite suddenly, so always be cautious when driving or operating machines at night.
- /.../ can cause muscle and joint pain. Cut down on intensive exercise and physical activity.
- /…/ may increase blood fats, such as cholesterol and triglycerides. Your doctor will test these levels before, during and after /.../ treatment. Tell your doctor if you already have high blood fats. If your blood fats stay high, your doctor may lower your dose, or discontinue your treatment with /.../.
- /…/ has been associated with inflammatory bowel disease. If you get severe (bloody) diarrhoea stop taking /.../ and immediately contact your doctor.
- /.../ may increase blood sugar levels. In rare cases, people become diabetic. Your doctor may monitor blood sugar levels during treatment, particularly if you already have diabetes, have high blood fat levels, are overweight, or are an alcoholic.
- Lasting headache can occur, along with feeling sick (nausea), being sick (vomiting) and change in your eyesight including blurred vision. These may be signs of benign intracranial hypertension, especially if /…/ is taken with antibiotics called tetracycline. Stop taking this medicine straight away and contact your doctor.

- Severe skin reactions (e.g. erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported with the use of isotretinoin. See further in Section 4, 'Possible side effects'.
- Allergic reaction might occur, such as rash and itchiness. Serious (anaphylactic) reactions could be: difficulty breathing or swallowing caused by sudden swelling of the throat, face, lips and mouth. Also sudden swelling of the hands, feet and ankles. If you develop an allergic reaction, stop taking /…/ and seek urgent medical advice.
- /…/ may increase liver enzyme levels. Your doctor will do blood tests before, during and after /…/ treatment to check these levels. If they stay high, your doctor may lower your dose or take you off of this medicine.

Mental health problems
You may not notice some changes in your mood and behaviour and so it is very important that you tell your friends and family that you are taking this medicine. They may notice these changes and help you quickly identify any problems that you need to talk to your doctor about.

Children and adolescents
The use of /…/ in children under the age of 12 is not recommended. This is because it is not known if it is safe or effective in this age group. Use in adolescents over 12 years of age only after puberty.

Other medicines and /…/
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

- Do not take vitamin A supplements while taking /.../. Taking both together may increase the risk of side effects.
- Do not take /.../ and tetracyclines (an antibiotic) concomitantly. Taking both together may cause high pressure within the cranial cavity with symptoms such as headache, nausea, vomiting, visual disturbances and swollen optical disk.
- Do not use any skin treatments for acne while taking /.../. It is fine to use moisturisers and emollients (skin creams or preparations that prevent water loss and have a softening effect on the skin).

Pregnancy and breast-feeding

You must not take /.../ if you are pregnant.

If pregnancy does occur during treatment with /.../ or in the month following, there is a great risk of very severe damage to the unborn baby.

Therefore you must use effective methods of contraception during and up to one month after /…/ treatment if you are a woman of childbearing potential (see section 2, 'Warnings and precautions').

If you do get pregnant while taking /.../ or in the month after you have stopped treatment, stop taking the medicine (if treatment is still ongoing) and inform your doctor immediately.

For more information on pregnancy and contraception, see section 2 "Pregnancy Prevention Programme".

You must not take /.../ if you are breast-feeding. The medicine is likely to pass into your milk and may harm your baby.

Driving and using machines
Your night vision may become impaired during your treatment. This can happen suddenly. In rare cases this has continued after the treatment has stopped. Drowsiness and dizziness have been reported very rarely. Caution is needed when driving or operating machines.

/…/ contains sorbitol, soya-bean oil and the colouring agent Cochineal red A
This medicine contains 5.3 mg sorbitol (on dried weight basis) in each 10 mg capsule and 17.0 mg sorbitol (on dried weight basis) in each 20 mg capsule.
/…/ contains soya-bean oil. If you are allergic to peanut or soya, do not use this medicinal product.
The colouring agent Cochineal red A (E124) may cause allergic reactions.

3. How to take /.../

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

/.../ capsules should be taken with food. Take the capsules once or twice daily.
Swallow them whole with a drink.

The recommended dose is:

Adults, adolescents and elderly
The usual starting dose is 0.5 mg per kilogram body weight per day (0.5 mg/kg/day).

After a few weeks your doctor may adjust your dose. This depends on how you are getting on with your medicine. For most patients the dose will be between 0.5 mg and 1.0 mg/kg/ day.
If you think that the effect of /.../ is too strong or too weak, talk to your doctor or pharmacist.

Children
/.../ should not be used in children under the age of 12 years.

Reduced kidney function
If you have severe kidney problems, you will usually start on a lower dose (such as 10 mg/day) which will be increased up to the highest dose your body can tolerate.

A course of treatment usually lasts for 16 to 24 weeks. Most patients only need one course. Your acne may continue to improve for up to 8 weeks after treatment. Usually you will not start another course until then.

Some people find their acne may worsen during the first weeks of treatment. It usually improves as treatment goes on.

If you take more /.../ than you should
Contact your doctor, emergency unit or pharmacist if you have taken more /.../ capsules than stated in this leaflet or more than your doctor has prescribed.
Symptoms of overdose include headache, nausea, vomiting, drowsiness, irritability and itching.

If you forget to take /.../
If you forget to take a dose, take one as soon as you remember, unless it is almost time to take your next dose. Then go on as before. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious and need immediate medical attention. If you notice any of the following side effects contact a doctor straight away:

Rare (may affect up to 1 in 1,000 people)
- Serious allergic/anaphylactic reactions with sudden swelling of the face, lips, mouth and throat with difficulty in breathing or swallowing, swelling of hands and feet. If you have a serious allergic reaction, get emergency medical help immediately

Very rare (may affect up to 1 in 10,000 people)
- Lasting headache with nausea, vomiting and blurred vision. These may be signs of 'benign intracranial hypertension', especially if /…/ is taken with antibiotics called tetracycline.
- Severe abdominal pain, with or without bloody diarrhoea, feeling sick (nausea) and vomiting. These can be signs of serious gut conditions
- Yellow skin or eyes, and feeling tired. These can be signs of hepatitis
- Muscle weakness which can be potentially life-threatening, may be associated with trouble moving arms or legs, painful, swollen, bruised areas of the body, dark-coloured urine, reduced or no urine output, confusion or dehydration. These are signs of rhabdomyolysis, a breakdown of muscle tissue which can lead to kidney failure
- Difficulty urinating (passing water), swollen and puffy eyelids, feeling excessively tired. These may be signs of kidney inflammation. Stop taking /…/ straight away and contact your doctor.

Frequency not known (cannot be estimated from the available data)
- Serious skin rashes (erythema multiforme, Stevens- Johnson syndrome, and toxic epidermal necrolysis). These appear initially as circular patches often with central blisters usually on arms and hands or legs and feet, more severe rashes may include blistering of the chest and back. Additional symptoms such as infection of the eye (conjunctivitis) or ulcers of the mouth, throat or nose may occur. Severe forms of rash may progress to widespread peeling of the skin which can be life threatening. These serious skin rashes are often preceded by headache, fever, body aches (flu-like symptoms). If you develop a rash or these skin symptoms, stop taking /.../ and contact your doctor immediately.

Mental problems
Rare effects (may affect up to 1 in 1,000 people):
- Depression or related disorders. Signs of this include sad or altered mood, anxiety, feelings of emotional discomfort
- Existing depression getting worse
- Becoming violent or aggressive

Very rare effects (may affect up to 1 in 10,000 people):
- Some people have had thoughts or feelings about hurting themselves or ending their own lives (suicidal thoughts), have tried to end their own lives (attempted suicide), or have ended their lives (suicide). These people may not appear to be depressed.
- Unusual behaviour.
- Signs of psychosis: a loss of contact with reality, such as hearing voices or seeing things that are not there.

Contact your doctor straight away if you get signs of any of these mental problems. Your doctor may tell you to stop taking /.../. That may not be enough to stop the effects: you may need more help, and your doctor can arrange this.

Other side effects:

Very common (may affect more than 1 in 10 people)
- Anaemia with symptoms such as weakness, dizziness and pale skin (if red blood cells are affected)
- Bruising, bleeding and clotting more easily (if clotting cells are affected)
- Dry skin, blushing skin, fragile skin, localised shedding of skin, itching, dry eyes, eye irritation, inflammation of skin, lips, eyes and/or eyelids
- Increased liver enzymes
- Pain in joints, muscles and back, particularly in teenagers

- Increased blood fat levels and decreased high density lipoprotein (HDL).

Common (may affect up to 1 in 10 people)
- Headache
- Dry nose, nosebleed, sore or inflamed throat and nose
- More liable to get infections due to lower white blood cell count
- Higher levels of cholesterol in the blood, increased blood glucose
- Blood or protein in the urine.

Rare (may affect up to 1 in 1,000 people)
- Allergic skin reactions with rash and itching. If you have any allergic reaction, stop taking /…/ and contact your doctor
- Hair loss.

Very rare (may affect up to 1 in 10,000 people)
- Bacterial infections of the skin and mucous membranes
- Lymph glands may become swollen
- Diabetes with symptoms such as excessive thirst and frequent need to urinate
- High levels of uric acid in the blood
- Swollen optic disk
- Convulsions, drowsiness, dizziness
- Nausea, generally feeling unwell
- Blurred vision, colour blindness and colour vision getting worse, cloudiness of the lens of the eye (cataract), clouding or scarring of the surface of the eye (corneal opacity), intolerance to contact lenses, decreased night vision, sensitivity to light may increase; you may find that you need to wear sunglasses to protect your eyes from bright sunlight, inflammation of the cornea (keratitis), visual disturbances
- Impaired hearing
- Inflammation of the blood vessels (sometimes with bruising, red patches)
- Sudden tight chest, shortness of breath and wheezing, particularly if you have asthma
- Hoarseness, dry throat
- Severe acne (acne fulminans), acne can get worse, skin redness (especially of the face), skin eruption (exanthema), hair disorder, increased body hair, bacterial infections at the base of the nail, changes to nails, sensitivity to light, discolouring of the skin, red raised bumps on the skin which bleed easily (pyogenic granuloma), excessive sweating
- Arthritis
- Bone disorders (delayed growth, extra growth and changes to bone density), calcium deposits in soft tissue, sore tendons
- Increased formation of granulation tissue (which may cause thickened scarring)
- Increased blood creatine phosphokinase (sign of high levels of muscle breakdown products in your blood)

Not known (cannot be estimated from the available data)
- Problems getting or maintaining an erection
- Lower libido

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist.This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store /.../

Keep this medicine out of the sight and reach of children.

Keep the blister in the outer carton in order to protect from light.

Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What /.../ contains

- The active substance is isotretinoin. Each soft capsule contains 10 mg isotretinoin or 20 mg isotretinoin.
- The other ingredients are:
  Capsule content: Refined soya-bean oil, all-rac-alpha-tocopherol (E 307), disodium edetate (385), butylhydroxyanisole (BHA E 320) , hydrogenated vegetable oil, soya-bean oil (partly hydrogenated), yellow beeswax.
  Capsule shell: 10 mg capsules: Gelatine, glycerol, sorbitol, purified water, Cochineal red A (E124) , black iron oxide (E172), titanium dioxide (E 171). *20 mg capsules:* Gelatine, glycerol, sorbitol, purified water, Cochineal red A (E124) , indigocarmine (E 132), titanium dioxide (E 171).

What /.../ looks like and contents of the pack
/.../ 10 mg capsules: Light violet coloured, oval, soft, gelatine capsule, containing a yellow/orange opaque viscous liquid, 10 mm x 7 mm in size.
/.../ 20 mg capsules: Maroon coloured, oval, soft, gelatine capsule, containing a yellow/orange opaque viscous liquid, 13 mm x 8 mm in size.

The capsules come in blister packs of:
/.../ 10 mg: 10, 20, 30, 60, 90, 100 capsules.
/.../ 20 mg: 10, 20, 30, 60, 90, 100 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:

<[To be completed nationally]>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Denmark	Acnenor
Hungary	Inerta 10 mg, 20 mg lágy kapszula
Poland	Actaven
Sweden	Isotretinoin Actavis
Slovakia	Isotretinoin Actavis 10 mg
	Isotretinoin Actavis 20 mg

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

<[To be completed nationally]>

<Detailed and updated information on this product is available by scanning the QR code included in the PL with a smartphone. The same information is also available on the following URL: [URL to be included] <and the <NCA> website >>.

'QR code to be included' + <URL>