SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CURACNE 5 mg, soft capsule

CURACNE 10 mg, soft capsule

CURACNE 20 mg, soft capsule

CURACNE 40 mg, soft capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION CURACNE 5 mg, soft capsule

CURACNE 5 mg, soft capsule

Each soft capsule contains 5 mg isotretinoin.

Excipient with known effect:
52.1 mg soya-bean oil, refined per soft capsule.

For a full list of excipients, see section 6.1.

CURACNE 10 mg, soft capsule

Each soft capsule contains 10 mg isotretinoin.

Excipient with known effect:
104.2 mg soya-bean oil, refined per soft capsule.

For a full list of excipients, see section 6.1.

CURACNE 20 mg, soft capsule

Each soft capsule contains 20 mg isotretinoin.

Excipient with known effect:
208.4 mg soya-bean oil, refined per soft capsule.

For a full list of excipients, see section 6.1.

CURACNE 40 mg, soft capsules

Each soft capsule contains 40 mg isotretinoin.

Excipient with known effect:
191.50 mg soya-bean oil, refined per soft capsule.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, soft.

Each 5 mg capsule has a bi-coloured opaque red/brown and cream gelatin shell with a bright yellow/orange fill and is printed on one side with the logo “5”.

Each 10 mg capsule has a red/brown gelatin shell with a bright yellow/orange fill and is printed on one side with the logo “I 10”.

Each 20 mg capsule has a bi-coloured opaque red/brown and cream gelatin shell with a bright yellow/orange fill and is printed on one side with the logo “I 20”.

Each 40 mg capsule has an orange/brown opaque gelatin shell with a bright orange/yellow fill and is printed on one side with the logo “I40”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe forms of acne (such as nodular and 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

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.

Posology

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 0.5-1mg/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 lower dose (e.g. 10 mg/day). The dose should then be increased up to 1mg/kg/day or until the patient is receiving the maximum tolerated dose (see section 4.4 “Special warnings and special precautions for use”).

Patients with intolerance

In patients who show severe intolerance to 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.

Paediatric population

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

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 "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 special precautions for use").

Isotretinoin is also contraindicated in patients:

- With hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- With hepatic insufficiency
- With excessively elevated blood lipid values
- With hypervitaminosis A
- Allergic to peanut or soya bean oil as Curacné contains soya bean oil
- Receiving concomitant treatment with tetracyclines (see section 4.5 "Interaction with other medicinal products and other forms of interactions")
- Receiving vitamin A
- Receiving others retinoids (acitretin, alitretinoin)

4.4 Special warnings and special precautions for use

Teratogenic effects

Isotretinoin is a powerful human teratogen inducing a high frequency of severe and lifethreatening birth defects.

Isotretinoin must never be used in:

- Pregnant women

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

Pregnancy Prevention Programme

Patients information: Istotretinoin 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 antibacterial 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, 4 weeks before starting treatment, throughout the entire duration of treatment and 4 weeks after the end of treatment. At least one and preferably two complementary forms of contraception including a barrier method should be used.
- Even if she has amenorrhoea she must follow all of the advice on effective contraception.
- She should be capable of complying with effective contraceptive measures.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.
- She understands the need and accepts to undergo pregnancy testing before, every 4 weeks 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.

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 4 weeks prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 4 weeks 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 in the patient's file.

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.

Women of childbearing potential must use at least one effective method of contraception for at least 4 weeks prior initiation of therapy, during therapy and during 4 weeks after isotretinoin therapy.

Preferably the patient should use two complementary forms of contraception including a barrier method (condoms).

Pregnancy testing

Medically supervised plasmatic pregnancy tests with a minimum sensitivity of 25 mlU/mL must be performed for women of childbearing potential in the first 3 days of the menstrual cycle, as described below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence.

<u>Prior to starting therapy:</u>

In order to exclude the possibility of pregnancy prior to starting contraception, 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 must be performed during the consultation when isotretinoin is prescribed or in the 3 days prior to the visit to the prescriber once the patient had been using effective

contraception for at least 4 weeks. This test should ensure the patient is not pregnant when she starts treatment with isotretinoin.

Follow-up visits

A medically supervised plasmatic pregnancy test must be repeated every 4 weeks. These pregnancy tests must be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber. Follow-up visits should be arranged at 28 day intervals.

End of treatment

A medically supervised pregnancy test must be performed five weeks after stopping treatment to exclude pregnancy.

Prescribing and dispensing restrictions

For women of childbearing potential, prescriptions of isotretinoin should be limited to 4 weeks 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

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

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

Additional precaution

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 4 weeks 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, women of childbearing potential and to male patients.

Psychiatric disorders

Depression, depression aggravated, anxiety, aggressive tendencies, mood alteration, psychotic symptoms and, very rarely, suicidal ideations, 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 subcutaneaous 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 dermabraison 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.

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.

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 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 “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”). 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 months 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 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 800 mg/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) diarrhea 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.

4.5 Interaction with other medicinal products and other forms of interaction

Associations contraindicated:

+ Vitamin A due to the risk of developing hypervitaminosis A

+ Others retinoids (acitretin, alitretinoin) due to the risk of developing hypervitaminosis A

+ Cyclines

Cases of intracranial hypertension 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 special precautions for use").

Concurent administration of isotretinoin with topical keratolytic or exfoliative antiacne agents should be avoided as local irritation may increase.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 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.

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.

Women of childbearing potential / Contraception:

Women of childbearing potential must use at least one effective method of contraception for at least 4 weeks prior initiation of therapy, during therapy and during 4 weeks after isotretinoin therapy. (see section 4.4)

Preferably the patient should use two complementary forms of contraception including a barrier method (condoms).

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 special 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.

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 the safety Profile

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.

Tabulated list of adverse reactions

Adverse reactions are classified as listed below by MedDRA Systems Organ Class and frequency. Frequency is defined using the following convention: listed below as very common (≥ 1/10), common (≥ 1/100 and <1/10), uncommon (≥ 1/1,000 and <1/100), rare (≥ 1/10,000 and <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data).

Infections :	
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 alteration
Very Rare	Abnormal behaviour, Psychotic disorder, Suicidal ideation, Suicide attempt, Suicide
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	Visual disturbances, Blurred vision, Cataract, Colour blindness (colour vision deficiencies), Contact lens intolerance, Corneal opacity, Decreaded night vision, Keratitis, Papilloedema (as sign of benign intracranial hypertension), Photophobia
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, haermorrhagic diarrhoea and inflammatory bowel disease, Nausea, Pancreatitis (see section 4.4 "Special warnings and special precautions for use").
Hepatobiliary disorders :	
Very common	Transaminase increased (see section 4.4 " Special warnings and special precautions for use")
Very Rare	Hepatitis
Skin and subcutaneous tissues disorders :	
Very common	Cheilitis, Dermatitis, Dry skin, Localised exfoliation, Pruritus, Rash erythematous, Skin fragility and (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.
Musculo-skeletal 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
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

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

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.

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 case of accidental 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: 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 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 form 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. The liver cell changes observed with vitamin A did not occur with isotretinoin.

All observed side effects of hypervitminosis 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 teratogenic and embryotoxic.

Due to the teratogenic 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 special 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. hydrogenated vegetable oil, beeswax yellow.

Curacne 5 mg, 20 mg and 40 mg: Composition of the capsule shell: gelatin, glycerol, purified water, red iron oxide (E172), yellow iron oxide (E172), titanium dioxide 25% (E171) in glycerol.

Curacne 10 mg: Composition of the capsule shell: gelatin, glycerol, purified water, red iron oxide (E172),

Composition of the black ink: SDA 35 Alcohol, Propylene Glycol, Black Iron Oxide, Polyvinyl Acetate Phthalate, Water, Isopropyl Alcohol, Polyethylene Glycol, Ammonium Hydroxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container. Keep the container tightly closed to protect from light.

6.5 Nature and contents of container

Curacne 5 mg, 10 mg, 20 mg: 28, 30, 50, 56 and 60 soft capsules in thermoform blister (PVC/PE/PVDC) sealed with aluminium lidding foil. Not all pack sizes may be marketed.

Curacne 40 mg:

Blister PVC/PE/PVDC/Aluminium. Blister pack of 30 capsules, soft.

6.6 Instructions for use, handling and disposal

At the end of treatment male and female patients must return any unused capsules to their pharmacist.

7. MARKETING AUTHORISATION HOLDER

PIERRE FABRE DERMATOLOGIE
45, place Abel Gance
92100 BOULOGNE
FRANCE

PACKAGE LEAFLET

Information for the user CURACNE 5, 10, 20, 40 mg Isotretinoin

Read all of this leaflet carefully before you start using 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 CURACNE is and what it is used for

CURACNE contains isotretinoin, which is the active substance, belonging to a class of medicines known as retinoids.

CURACNE is indicated for the treatment of severe acne (such as nodular and conglobate acne or acne liable to cause permanent scarring) resistant to both standard therapy with oral antibiotics and local therapy (cream, gel, ointment or lotion).

CURACNE should only be prescribed by and under the supervision of physicians with experience in use and monitoring retinoids in the treatment of severe acne.

CURACNE is not indicated for the treatment of acne occurring before puberty and is not recommended for children aged less than 12 years old.

2. What you need to know before you take CURACNE

Do not take CURACNE if:

- You are pregnant or breast-feeding, if you intend to become pregnant, or if you are of childbearing potential and you are not taking all the measures imposed by this treatment to prevent pregnancy **(see box "Pregnancy and breast-feeding, Important" below)**.
- You are allergic to isotretinoin or any other ingredients of this medicine (listed in section 6), especially peanuts, or soya.
- You have hepatic insufficiency (serious disease of the liver).
- In the event of hypervitaminosis A (very high vitamin A level in the body).
- You have high blood lipid level (cholesterol, triglycerides).
- You are taking an antibiotic of the tetracycline family.

- You are taking vitamin A or other retinoids (acitretin, alitretinoin)

Warnings and precautions

Talk to your doctor or pharmacist before taking CURACNE if:

- You have a history of depression or other mental problems (see chapter 4: possible side effects).
- You have problems with your kidneys. Your doctor may adjust the isotretinoin dosage.
- You are overweight or have diabetes mellitus, high blood levels of cholesterol or triglycerides, or a high alcohol consumption.

  In these cases, an elevation in blood lipid and glyceride levels may be observed.

  If you are in one of these situations, your doctor may prescribe regular blood tests.

  Monitor your blood glucose levels more closely throughout the duration of treatment if you have diabetes mellitus.

- You have problems with your liver.

  CURACNE can increase your transaminase levels (hepatic enzymes). Your doctor will prescribe regular blood tests, before and during the treatment, to check the state of your liver.

  Persistent elevation of these enzymes may result in your doctor's reducing the CURACNE dosage or discontinuing treatment.

- You have a history of intestinal disorders

Stop the treatment immediately and notify a doctor rapidly if:

- You become pregnant during the treatment or in the month following discontinuation of the treatment.
- You experience:
  - Difficulty in breathing, itching and/or skin rash.

    These symptoms may be due to an allergic reaction.
  - Headache with nausea, vomiting or impaired vision.
  - Severe stomach pain, nausea or vomiting, or severe diarrhoea with blood in your stools.
  - Difficulty in urinating or even inability to urinate.
  - Impaired night vision and/or visual disorders.
  - Psychiatric disorders, in particular signs of depression (feeling very sad or having crying spells, thinking about hurting yourself or withdraw from family or friends).
- You notice a yellowing of the eyes or skin and a feeling of dizziness.

Special warnings for female patients:

Use during pregnancy and breast-feeding:

Use of CURACNE is totally forbidden during pregnancy and breast-feeding (see box "Pregnancy and breast-feeding, Important" below).

Pregnancy and breast-feeding, Important

Pregnancy and breast-feeding are an absolute contraindication to treatment with isotretinoin

CURACNE is teratogenic. This means that if you become pregnant during treatment or during the month following treatment, this medicine may cause **serious malformations in your unborn child**:

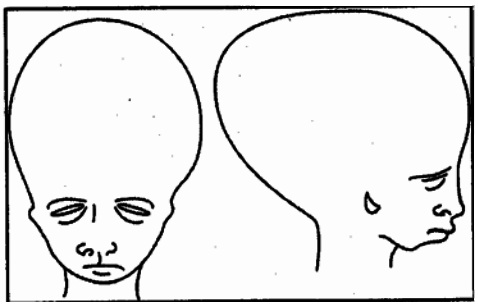

Diagram of possible **external malformations** in the event of pregnancy during treatment with isotretinoin: No ear(s) or ears attached low down, large head and small chin, eye abnormalities, palate malformations.

Internal malformations also frequently occur. These concern the heart, the thymus, the nervous system, and the parathyroid gland. This drug may also induce miscarriage.

You must not take CURACNE if:

- You are pregnant or if you intend to be pregnant during your treatment or during the month following discontinuation of the treatment.
- You are breast-feeding, because isotretinoin may pass into your breast milk and harm your baby.

PREGNANCY PREVENTION PROGRAMME

Curacne is contraindicated in woman of child bearing potential, unless all of Pregnancy Prevention Programme are met.

CURACNE prescription and delivery conditions for women of childbearing potential:

- You have understood the teratogenic risk.
- You have understood why you must not become pregnant.

  Your doctor has given you information on the measures to be taken in order to avoid becoming pregnant and has given you a brochure explaining the various methods of contraception.

  If necessary, your doctor may refer you to a gynæcologist.

- You have agreed to use at least one and preferably two effective method of contraception, , including a barrier method:
  - **for at least 1 month before beginning CURACNE treatment**,
  - **throughout the duration of treatment,**
  - **for 1 month after the end of treatment.**

  You must use contraception even if you are not sexually active or if you do not have menstrual periods.

- You understand the need for a medical follow-up every month and agree to this. In this context, you will be prescribed pregnancy tests by your doctor:
  - **before starting CURACNE. The test is to be conducted during the first**
  - **3 days of the menstrual cycle (period).**
  - **each month during the treatment,**
  - **and 5 weeks after stopping it.**

  The result of each test must be negative: You must not become pregnant at any time during treatment or in the month following treatment.

- You must sign (yourself or the adult responsible for you) a consent form concerning treatment and contraception, considering that:
  - You have been informed of the risks associated with CURACNE treatment,
  - You agree to comply with Pregnancy Prevention Program.

Special warnings for male patients:

There are no particular conditions for prescribing this drug to male patients: there is no evidence suggesting that the fertility or offspring of male patients will be affected by their taking isotretinoin. Remember that you should not pass on your medicine to anyone else, especially to woman.

Other medicines and CURACNE:

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Do not take a medicine containing vitamin A, or tetracyclines during CURACNE treatment.

Concurent administration of isotretinoin with topical keratolytic or exfoliative antiacne agents should be avoided as local irritation may increase.

Driving and using machines:

Be careful when driving or using machines at night, your night vision may be impaired while on this treatment, sometimes abruptly.

The impairment seldom persists after treatment discontinuation.

CURACNE contains soya-bean oil:

Do not take this medicine in you are allergic to peanuts or soya.

Advice for daily life:

- Apply moisturising ointments or creams to your skin and use a lip balm during treatment if you experience dryness of the skin or lips.
- In general, avoid applying any irritant product to the skin (for example: peeling cream) during treatment.
- Avoid excessive exposure to the sun: CURACNE may increase sensitivity to the sun during treatment.
- Apply a sunscreen cream (SPF of at least 15) if, nevertheless, exposure to the sun cannot be avoided.
- Do not use UV lamps or sun tanning beds or booths.
- Avoid wax depilation during and for at least 6 months after treatment discontinuation. Also avoid surgical dermabrasion or laser therapy (cosmetic procedures designed to smooth your skin to diminish scars or aging signs). These procedures may cause skin scarring, hypo/hyperpigmentation (discoloration or high coloration of the skin) or detachment of the epidermis.
- Wear glasses rather than contact lenses throughout the treatment if you experience very dry eyes.
- You may need to wear sunglasses to protect your eyes from being dazzled.
- Always be careful when driving or operating machines at night, because visual changes (impaired night vision) occur abruptly.

- Refrain from strenuous physical exercise during treatment with CURACNE because pain in your joints or muscles may sometimes occur during treatment.
- Refrain from donating blood during treatment and for one month after treatment discontinuation. If a pregnant woman were to receive your blood, her baby could be born with serious malformations.

3. How to take CURACNE

Dosage:

Always take CURACNE as your doctor has told you. You should check with your doctor or your pharmacist if you are not sure.

The usual starting dose is 0.5mg per kilogram bodyweight per day (0.5 mg/kg/day).

For most patients the dose will be between 0.5 and 1.0 mg/kg/day.

If you have the impression that the effect of Curacne is too strong or too weak, talk to your doctor.

The capsules should be taken once or twice a day during a meal. Swallow the capsules whole without chewing or sucking them.

Patients with severe renal insufficiency

In patients with severe renal insufficiency, treatment should be started at lower dose (e.g. 10 mg/day).

Use in children

Curacne 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 recommended dose, your doctor may continue treatment at the highest tolerated dose.

Duration of treatment:

A course of CURACNE lasts 16 to 24 weeks. Your skin may continue to improve for up to 8 weeks after the end of treatment.

Therefore wait at least until this period of 8 weeks has elapsed before beginning a new course of treatment, if necessary. Most patients only need one course of treatment.

If you take more CURACNE than you should:

If you have taken more CURACNE than you should, you may suffer from hypervitaminosis A, manifested by intense headaches, nausea or vomiting, sleepiness, irritability and itching.

Contact your doctor, your pharmacist or the nearest hospital as soon as possible.

If you forget to take CURACNE:

If you have forgotten a dose of CURACNE, do not take a double dose to make up for the forgotten dose.

Then, resume your usual dosing schedule.

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

4. Possible side effects

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

These effects often regress during treatment or after treatment discontinuation or dosage modification (speak to your doctor about this). Your doctor can help you deal with the situation.

Some side effects can be serious

- On rare occasions, some patients taking isotretinoin, or soon after stopping isotretinoin, have become depressed or experienced aggravation of their depression, or have developed other serious mental problems.

  Symptoms include sadness, anxiety, mood changes, crying spells, irritability, loss of pleasure or interest in sports or social activities, sleeping too much or too little, changes in weight or appetite, diminished school or work performance or problem in concentrating.

  In very few cases, some patients have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts), sometimes taking action. There have been reports that some of these patients did not appear to be depressed.

  Very rarely, there have been reports of patients on CURACNE becoming aggressive or violent.

  Tell your doctor if you have a history of any mental illness including depression, suicidal behaviour or psychosis (loss of contact with reality, such as hearing voices or seeing things that are not there), or if a member of your family suffers or has suffered from a mental problem.

  Tell your doctor if you take any medicines for one of these conditions.

  If you think that you are developing any of these mental conditions, contact your doctor right away. You may be advised to stop taking isotretinoin.

  However, stopping isotretinoin may not be sufficient to relieve your symptoms and you may need further help which your doctor can arrange.

- Sudden life-threatening allergic reaction (anaphylactic reactions)

- Serious skin rashes (erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), which are potentially life-threatening and require immediate medical attention. 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 CURACNE and contact your doctor immediately.

All other side effects are listed below by frequency.

Very common side effects: may affect more than 1 in 10 people

- Low red blood cell count (anaemia), low blood platelet count, increased platelet count.
- Increased sedimentation rate (a marker for acute inflammation).
- Fatty acid increased (blood triglicerides increase), fat to protein ratio decreased (high density lipoprotein decreased),
- Elevated liver enzymes (transaminases increased)

Accordingly, your doctor may have to prescribe blood tests and take the necessary measures.

- Red sores or deep cracks at the corners of the mouth or lips, inflammation of the skin, dry skin, localised desquamation, itchiness, red eruption of the skin, skin fragility.
- Inflammation of the eyelids, discharge with itching of the eyes and crusty eyelids (conjunctivitis), eye irritation and dryness of the eyes.
- Back pain, muscle and joint pains. It is therefore prudent to reduce strenuous physical exercise during treatment. All these effects are reversible following treatment discontinuation.

Common side effects: may affect up to 1 in 10 people

- Elevation of blood glucose and a type of fat (cholesterol), presence of proteins or blood in the urine.
- Low white blood cell count that can make you more prone to infection.
- Headache.
- Nasal dryness, nosebleed and rhinopharyngitis.

Rare side effects: may affect up to 1 in 1,000 people

- Allergic skin reactions, hypersensitivity.
- Hair loss (alopecia)

Very rare side effects: may affect up to 1 in 10,000 people

- Inflammation of the pancreas, or gastrointestinal haemorrhage or inflammatory bowel disease. In the event of violent pain in the abdomen, with or without bloody diarrhoea, nausea and vomiting, stop taking isotretinoin and contact your doctor as soon as possible.
- Liver disease (hepatitis) including nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes.
- Kidney disease including severe tiredness, difficulty urinating or even inability to urinate and swollen eyelids. If you experience these symptoms while on isotretinoin, stop taking the treatment and contact your doctor.
- Too high level of sugar in the blood (diabetes), with symptoms including excessive thirst, the passing of a greatly increased amount of urine, increase in appetite with a loss of weight, feeling tired, drowsy, weak, depressed, irritable and generally unwell. In this case, contact your doctor.

- Benign intracranial hypertension has occurred in patients concomitantly taking isotretinoin and certain antibiotics (tetracycline).

  This hypertension expresses itself by persistent headaches with nausea, vomiting or blurred vision. Stop taking CURACNE and contact your doctor as soon as possible.

- Seizures (convulsions).
- Narrowing or blockage of blood vessels.
- Worsening of acne over the first few weeks of treatment with inflammatory lesions on the skin, severe form of acne (acne fulminans).

  However, in general, pursuit of treatment will be accompanied by alleviation of acne and other symptoms.

- Inflammation of the colon.
- Localised bacterial infection may occur.
- Facial erythema, skin rash.
- Hair disorders, abnormal hairiness, nail plate abnormalities, hangnail infected.
- Benign vascular lesions of the skin and mucosa.
- Increased sensitivity to the sun (photosensitivity reaction, see advice for daily life, chapter 2).
- Increased pigmentation, excessive sweating.
- Increase volume of lymph nodes.
- High uric acid levels in the blood which may cause gout.
- The medicine may impair night vision and visual disorders may occur abruptly. Such effects rarely persist after the end of treatment.
- Impaired colour vision, intense ocular irritation, corneal opacities, irritation or feeling of having something in the eye (keratitis), blurred vision, difficulty seeing (cataracts), increased sensitivity to light, visual disturbances, and poor tolerance of contact lenses. You may need sunglasses to protect your eyes from being dazzled.

  If the medicine causes you to have the slightest difficulty in seeing, inform your doctor rapidly.

- Impaired hearing.
- Dry throat, nausea, an abnormal change in voice (hoarseness).
- Malaise.
- Disease mainly affecting the joints with pain and swelling, bone anomalies, retarded growth and reduced bone density, soft tissue calcification, inflammation of tendon. The blood levels of an enzyme (creatine phosphokinase) released during muscle fibre degradation may be increased in the event of strenuous physical exertion in patients on isotretinoin, breakdown of muscle which can lead to kidney problems.
- Drowsiness, Dizziness

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 CURACNE

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

Do not use after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Do not store above 25°C. Store in the original container. Keep the container tightly closed to protect from light.

When you have finished your treatment, you must return all the remaining capsules to your pharmacist.

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 CURACNE contains

CURACNE 5 mg, 10 mg, 20 mg, 40 mg, soft capsule

- The active substance is:

For a soft capsule of 5 mg: isotretinoin ..... 5 mg

For a soft capsule of 10 mg: isotretinoin ..... 10 mg

For a soft capsule of 20 mg: isotretinoin ..... 20 mg

For a soft capsule of 40 mg: isotretinoin ..... 40 mg

- The other ingredients are: soya-bean oil refined, hydrogenated vegetable oil, beeswax yellow.

Composition of the capsule shell of 5 mg, 20 mg and 40 mg: gelatin, glycerol, purified water, red iron oxide (E172), yellow iron oxide (E172), titanium dioxide 25% (E171) in glycerol.

Composition of the capsule shell of 10 mg: gelatin, glycerol, purified water, red iron oxide (E172).

Composition of the black ink: SDA 35 Alcohol, Propylene Glycol, Black Iron Oxide, Polyvinyl Acetate Phthalate, Water, Isopropyl Alcohol, Polyethylene Glycol, Ammonium Hydroxide.

What CURACNE looks like and contents of the pack

This medicine is supplied in the form of soft capsules in boxes of 30.

Each 5 mg capsule has a bi-coloured opaque red/brown and cream gelatin shell with a bright yellow/orange fill and is printed on one side with the logo “5”.

Each 10 mg capsule has a red/brown gelatin shell with a bright yellow/orange fill and is printed on one side with the logo “I 10”.

Each 20 mg capsule has a bi-coloured opaque red/brown and cream gelatin shell with a bright yellow/orange fill and is printed on one side with the logo “I 20”.

Each 40 mg capsule has an orange/brown opaque gelatin shell with a bright orange/yellow fill and is printed on one side with the logo “I40”.

Marketing Authorisation Holder: PIERRE FABRE DERMATOLOGIE - 45 place Abel Gance - 92100 Boulogne - France
Distributor: PIERRE FABRE DERMATOLOGIE - 45 place Abel Gance - 92100 Boulogne - France
Manufacturer: CATALENT FRANCE BEINHEIM S.A. - 74, rue Principale - 67930 Beinheim - France
This leaflet was revised on May 21st 2015.

Prescription and delivery conditions:

CURACNE is a prescription-only medicine, that is a medicinal product requiring special monitoring during treatment.

For women of childbearing potential:

- Prior to prescription, the patient’s consent to care and contraception is to be obtained.
- The prescription duration is limited to one month of treatment. Pursuit of treatment requires a new prescription.
- The treatment is to be dispensed, at the latest, 7 days after the date of prescription.
- Treatment will only be dispensed when the presence of the following mandatory statements on the prescription has been checked:
    - For the first prescription:
        - Signature of the care and contraception consent form.
        - Use of at least one effective method of contraception, stated at least one month previously.
        - Assessment of the patient’s degree of understanding.
        - Date of the pregnancy test (plasma hCG).
    - For subsequent prescriptions:
        - Pursuit of effective contraception.

- Assessment of the patient's degree of understanding.
- Date of the last pregnancy test (plasma hCG).

You can obtain further information on CURACNE from your doctor or pharmacist.