PACKAGE INSERT:

ACNETRET 10 CAPSULES

ACNETRET 20 CAPSULES

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

ACNETRET 10 CAPSULES

ACNETRET 20 CAPSULES

This product is teratogenic. It should not be taken by pregnant women, women intending to become pregnant, or sexually active women in their fertile years, not using at least two methods of contraception, as severe malformations may occur during pregnancy.

COMPOSITION

ACNETRET 10 : Each capsule contains isotretinoin 10 mg.

ACNETRET 20 : Each capsule contains isotretinoin 20 mg.

The inactive ingredients are: Beeswax white, butylated hydroxyanisole (antioxidant), disodium EDTA, partially hydrogenated vegetable oil, soyabean oil, gelatin, glycerin, sorbitol 70% solution, carmoisine, brilliant blue, ponceau 4R, iron oxide black, titanium dioxide and purified water.

PHARMACOLOGICAL CLASSIFICATION

A 13.4.2 Dermatological preparations – other.

PHARMACOLOGICAL ACTION

Isotretinoin is a synthetic stereoisomer of all-trans retinoic acid (tretinoin). The exact mechanism of action of isotretinoin is unknown.

Pharmacokinetics:

After oral administration, isotretinoin is well absorbed from the gastrointestinal tract with peak concentrations reached within about 2 to 4 hours. Oral bioavailability in the fasting state is approximately 20 %. The presence of food substantially increases the extent of systematic absorption. Enterohepatic circulation may play a role in the pharmacokinetics in humans. Peak plasma concentration in acne patients ranges from 98 to 535 nanograms/ml following an 80 mg dose. Steady state blood concentration for isotretinoin is 160±19 nanograms/ml following doses of 40 mg twice daily. Isotretinoin is extensively bound to plasma proteins, primarily albumin (99.9 %). Isotretinoin is metabolized in the liver.

4-oxo-isotretinoin is the major metabolite of isotretinoin. The half-life of isotretinoin in plasma ranges between 10 to 20 hours. The mean elimination half-life of the major metabolite, 4-oxo-isotretinoin, is 25 hours (range 17 to 50 hours). Elimination is billiary (faeces) and renal.

INDICATIONS

ACNETRET should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systematic antibiotics.

CONTRA-INDICATIONS

- Hypersensitivity to isotretinoin or to any of the ingredients of **ACNETRET.**
- Pregnancy and Lactation.

ACNETRET should not be given to breastfeeding women.

ACNETRET causes fetal malformations. These fetal malformations have been documented and include hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent auditory canals), microphthalmia, cardiovascular abnormalities, facial dysmorphia, thymus gland abnormalities, parathyroid hormone deficiency and cerebellar malformations. There is also an increased risk of spontaneous abortion.

ACNETRET is therefore contra-indicated, not only in women who are pregnant or who may become pregnant while undergoing treatment, but also in all women of childbearing potential, unless an effective contraceptive is used, without any interruption, for one month prior to therapy, the duration of therapy and for at least one month after discontinuation of therapy.

Even female patients who normally do not employ contraception because of a history of infertility (except in the case of hysterectomy) or who claim absence of sexual activity, must be advised to use effective contraceptive measures while taking ACNETRET, following guidelines. It is recommended that two reliable forms of contraception be used simultaneously.

ACNETRET is contra-indicated in women of child-bearing potential unless the patient meets all the following conditions:

1. **The patient must have severe nodular acne, resistant to standard therapies**
2. **She must be informed by her physician of the hazards of becoming pregnant during, and one month after, treatment with ACNETRET.**
3. **She must be warned of the possibility of contraception failure**
4. **She must confirm that she has understood the precautions.**
5. **She must be reliable in understanding and carrying out instructions**
6. **She must be capable of complying with the mandatory effective contraceptive measures**
7. **She must use effective contraception, without interruption, for one month prior to therapy, the duration of therapy and for one month after discontinuation of therapy. Additional methods of contraception may be advised, particularly in the first cycle of hormonal contraception.**
8. **She must have a negative result from a reliable pregnancy test within eleven days prior to start of therapy. Monthly repetition of pregnancy testing is recommended during therapy.**
9. **She must start ACNETRET therapy only on the 2nd or 3rd day of the next normal menstrual period.**
10. **In the event of relapse treatment, she must use the same uninterrupted and effective contraceptive measures, one month prior to, during, and for one month after ACNETRET therapy, and the same reliable pregnancy evaluations should be followed.**

11. **She must fully understand the precautions and confirm her understanding and her willingness to comply with reliable contraceptive measures as explained to her.**

Should pregnancy occur, in spite of these precautions during treatment with ACNETRET during the first month after discontinuation, there is an extremely high risk of severe malformation of the fetus (involving in particular, the central nervous system, the heart and the large blood vessels), even after exposure for short periods only. Every possible precaution must be taken to ensure that the patient is not pregnant at the time of commencement of, during the course of and for one month after discontinuation of ACNETRET therapy.

In order to assist prescribing physicians and patients in avoiding fetal exposure to isotretinoin, the manufacturer provides a Pregnancy Prevention Program consisting of the following material to reinforce the warnings about the medicine's teratogenicity and emphasise the mandatory need for reliable contraception in female patients of childbearing potential:

1. **Patient information brochure**
2. **Brochure on birth control**
3. **Female patient information and consent form**
4. **Physician's guide to prescription**
5. **Physician's checklist for prescription to females**

The pregnancy prevention information should be given to patients both orally and in writing.

The Patient Information Brochure must be provided to all patients. In addition, all female patients must receive the Brochure on Birth Control and the Female Patient Information and Consent Form.

- Pre-existing Hypervitaminosis A.
- Hepatic and renal insufficiency.
- Patients with excessively elevated blood lipid values.
- Concurrent therapy with tetracyclines (See INTERACTIONS).

WARNINGS

ACNETRET is a scheduled medicine, not a cosmetic agent. It is a criminal offence to transfer it to or share it with any person not in possession of a valid prescription.

ACNETRET should only be prescribed by physicians experienced in the use of systematic retinoids and who understand the risk of teratogenicity associated with isotretinoin therapy. All patients should be given a copy of the patient information brochure.

Hepatitis which may be fatal may occur with **ACNETRET** therapy. Liver function should be evaluated before and one month after the start of therapy with **ACNETRET** and thereafter at three-monthly intervals. Elevations of liver enzymes have been reported with **ACNETRET** therapy, some of which normalised with dosage reduction or with continued administration. If normalisation does not occur or if hepatitis is suspected during treatment, **ACNETRET** should be discontinued and the aetiology further evaluated.

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 the use of **ACNETRET.** These events may be serious and result in hospitalization, disability, life threatening events or death. Patients should be monitored closely for severe skin reactions and the use of **ACNETRET** should be discontinued if these events occur.

ACNETRET should be used with caution in:-

- Patients with a history of depression – **ACNETRET** may cause depression, psychosis and rarely, suicidal ideation and suicide. Patients should be monitored for signs of depression and referred for appropriate treatment.
- Hypercholesterolaemia and patients with a tendency to develop hypertriglyceridaemia (e.g. those with diabetes mellitus, obesity, alcoholism or a family history of hypertriglyceridaemia) – Blood lipid determinations should be performed before therapy with **ACNETRET** and at regular intervals until the lipid response to **ACNETRET** is established, usually within one month of therapy. Approximately 25 % of patients experience a reversible elevation in plasma triglycerides, 15 % a reversible decrease in HDL-cholesterol and 7 % a reversible increase in total cholesterol.
- Diabetes mellitus – Frequent determinations of blood glucose levels are recommended.

ACNETRET therapy has been associated with:-

- Pseudotumor cerebri (benign intracranial hypertension) – Early signs and symptoms include papilloedema, headache, nausea, vomiting and visual disturbances. Patients presenting with these symptoms should be screened for papilloedema and, if present, discontinue therapy with **ACNETRET**. The patient should be referred to a neurologist.

- Visual impairment – Corneal opacities have occurred, especially with high doses. Patients experiencing visual difficulties should stop therapy and have an ophthalmological examination. A number of cases of decreased night vision have been reported. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night.
- Acute pancreatitis – Has been reported and may be associated with serum triglycerides in excess of 800 mg/dl.
- Skeletal:

  Skeletal hyperostosis – A higher prevalence of skeletal hyperostosis has been reported.

  Premature closure of the epiphysis may occur.
- Inflammatory bowel disease – Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should stop therapy with **ACNETRET**.

INTERACTIONS

Concurrent use of **ACNETRET** with vitamin A should be avoided. Patients should be advised against taking supplements containing vitamin A to avoid additive toxic effects from hypervitaminosis A.

Concurrent use of **ACNETRET** with tetracyclines is contra-indicated. Cases of benign intracranial hypertension have been reported with concomitant use. (See CONTRA-INDICATIONS.)

Concomitant therapy of **ACNETRET** and keratolytic or exfoliative anti-acne agents is not indicated. Adjuvant therapy with mild topical preparations may be given, if required.

Radiation therapy or ultraviolet therapy should not be undertaken during therapy with **ACNETRET**

No interactions between **ACNETRET** and oral contraceptives have been reported.

PREGNANCY AND LACTATION

ACNETRET is contraindicated in pregnancy and lactation (See CONTRA-INDICATIONS).

ACNETRET is teratogenic.

DOSAGE AND DIRECTIONS FOR USE

Patient response to **ACNETRET** is dose-related and varies from patient to patient. The dosage may require adjustment according to the severity of the condition and the occurrence of side-effects.

A transient worsening of acne has been reported, generally during the initial period of therapy with **ACNETRET**.

- Initial treatment dose: 0.5 mg/kg daily, maintained until the patient's response is clear (2 to 4 weeks).
- Maintenance dose: 0.5 to 1 mg/kg daily for a period of 12 to 20 weeks. Where the response to the initial dose is small and in severe cases, the daily dose may be increased to 1 mg/kg/day, provided that the medicine is well tolerated. The maximum dosage of 1 mg/kg per day should only be given for a limited period of time.

The daily dose may be taken with meals or with milk. Lower doses may be given as once-daily doses while higher doses may be administered twice or more times daily.

Treatment may be maintained at a lower dose in patients who show severe intolerance to the normal dose, with the end-result of a longer duration of therapy with **ACNETRET**. A cumulative dose of at least 120 mg/kg per treatment has been shown to increase remission rates and prevent relapse. The duration of therapy depends on the daily dose. A single course of therapy for 16 to 24 weeks has been shown to result in complete and prolonged remission in many patients. If a second course is needed, it should not be initiated until at least 8 weeks after completion of the first course as patients may continue to improve after discontinuation of **ACNETRET** therapy. Patients whose acne is not completely cleared at the end of the treatment can expect to show continuing improvement for several months after completion of therapy.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Most side-effects are dose-related.

Side-effects:

Haematological

- *Less frequent*: Anaemia, neutropenia, thrombocytopenia.

Central Nervous system

- Headache, malaise, drowsiness, pseudotumour cerebri (See Special precautions), seizures, behavioural disorders, depression, psychosis, suicidal ideation (rare).

Endocrine/Metabolic

- *Frequent:* Increases in triglycerides, total cholesterol and reductions in HDL cholesterol.
- *Less frequent:* Acute pancreatitis, hyperuricaemia.

Gastrointestinal

- Dry mouth, dryness of the pharyngeal mucosa (which can lead to hoarseness), bleeding gums, nausea, inflammatory bowel disease.

Kidney/Genitourinary

- Haematuria, proteinuria.

Liver

- *Frequent:* Reversible increases in transaminases.
- *Less frequent:* Hepatitis.

Musculoskeletal

- Muscle pain, joint pain, skeletal hyperostosis and premature closure of epiphysis (with high doses).

Ocular

- *Frequent:* Dry eyes, conjunctivitis, intolerance to contact lenses.
- *Less frequent:* Visual disturbances, loss of night vision, corneal opacities, keratatitis (possible related to dry eye syndrome).

Respiratory

- Bronchospasm.

Skin

- *Frequent:* Dry lips, dryness of the nose leading to nosebleeds, photosensitivity, peeling of skin on palms of hands or soles of feet.
- *Less frequent:* Dermatitis facialis, exanthema, pyogenic granuloma, paronychia, nail dystrophy, pruritus, sweating, increased formation of granulation tissue in acne

eruptions, hair thinning, alopecia, hirsutism, hyperpigmentation, allergic vasculitis, acne fulminans.

- *Frequency not known:* Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Other

Hearing deficiency, local or systematic infections with Gram-positive micro-organisms

Special precautions:

Intolerance to contact lenses may occur.

Patients should be advised not to donate blood during and for 1 month after stopping therapy with **ACNETRET**.

Excessive dermabrasion should be avoided in patients taking **ACNETRET** and for a period of 5 to 6 months after treatment because of the risk of hypertrophic scarring in atypical areas. Wax epilation should be avoided during therapy and for 5 to 6 months after therapy.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See SIDE-EFFECTS AND SPECIAL PRECAUTIONS)

Symptoms of overdosage:

Signs of hypervitaminosis A may occur in case of overdose.

Treatment of overdose:

Treatment is symptomatic and supportive. Evacuation of the stomach may be indicated in the first few hours after overdose.

IDENTIFICATION

ACNETRET 10:

Oval opaque purple colour soft gelatin capsules.

ACNETRET 20:

Oval opaque purple and white colour soft gelatin capsules.

PRESENTATION

The capsules are packed in aluminium – aluminium blisters of 60.

STORAGE INSTRUCTIONS

Store in a dry place below 25 °C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ACNETRET 10: 38/13.4.2/0267

ACNETRET 20: 38/13.4.2/0265

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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