SUMMARY OF PRODUCT CHARACTERISTICS

1.0 Name of the Medicinal Product

1.1 Product Name

ACNOTIN 20

1.2 Strength

Isotretinoin 20 mg

1.3 Description

Orange colour, oily suspension, filled in 6 minim, oval shaped, opaque purple, opaque white soft gelatin shell capsules.

2. Qualitative and Quantitative Composition

2.1 Qualitative Declaration

Recommended International Non-proprietary name (INN): Isotretinoin

2.2 Quantitative Declaration

Each softgel capsule contains:

Isotretinoin ……...20.00 mg

For full list of excipients, refer to section 6.1.

3. Pharmaceutical Form

Soft gelatin capsules.

4. Clinical Particulars

4.1 Therapeutic Indications

Isotretinoin is a retinoid for systemic treatment of acne. It is indicated for severe forms of nodulo-cystic acne which are resistant to previous therapy, particularly cystic acne and acne conglobata, especially when the lesions involve the trunk.

4.2 Posology and method of administration

Posology:

The usual adult and adolescent dose is 0.5 to 1 mg/kg of body weight per day (in two divided doses) for 15 to 20 weeks; the maximum recommended dose is 2 mg/kg of body weight per day and may be required in patients whose disease is very severe or is primarily located on the

chest or back instead of on the face. During the initial period of isotretinoin therapy, transient exacerbation of acne may occur; concomitant adrenocorticoid therapy may be required. Efficacy and side effects vary according to the individual patient; after about 4 weeks, therefore, dosage for the maintenance treatment should be adjusted within the range of 0.1 – 1 mg/kg daily to meet individual needs. Treatment usually lasts a total of 16 weeks. When assessing the results of the therapy, it should be borne in mind that there is often a further improvement after discontinuation of treatment. There should therefore be an interval of at least 8 weeks before re-starting treatment, which should be resumed in accordance with the previously mentioned dosage guidelines.

The capsules are taken with meals, low doses once daily, and higher amounts as a single dose or in several doses spread over the day.

Method of Administration: Oral

4.3 Contraindications

1. Hepatic and renal insufficiency: hypervitaminosis A; patients with excessively elevated blood lipid values; hypersensitivity to isotretinoin.
2. Blood donation by patients during and within 1 month of cessation of isotretinoin treatment to women of childbearing potential should be avoided.
3. Pregnancy, nursing Mother

4.4 Special Warnings and Precautions for Use

1. Isotretinoin should only be prescribed by physicians who are experienced in the use of systemic retinoids, preferably dermatologists, and understand the risk of teratogenicity if isotretinoin is used during pregnancy
2. Liver function should be checked before and 1 month after the start of treatment, and subsequently at 3-monthly intervals. Serum lipids (fasting value) should also be checked (before and 1 month after the start of therapy, and also at the end of the 3-to 4-month treatment period).
3. Depression, psychotic symptoms and rarely, suicide attempts and suicide have been reported in patients treated with isotretinoin. Although a causal relationship has not been established,

particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary.

4. Checking with physician anytime vision problems occur; wearing contact lenses may be uncomfortable. Vision impairment can occur including photophobia, blurred vision, or dryness of eyes. Vision problems can make driving a car or operating machinery dangerous.

5. A careful evaluation of the risk/benefit ratio should be carried out in every patient and isotretinoin administration should be restricted to severe cases.

6. Since acne is an androgen-dependent disease, contraceptives containing an androgen progestational substance, such as one derived form 19-nortestosterone (norsteroid), particularly in the presence of gyneco-endocrinological problems should be avoided.

7. Dermabrasion should be avoided in patients on isotretinoin and for a period of 5-6 moths after treatment because of the risk of hypertrophic scarring in atypical areas.

8. Wax epilation should be avoided in patients on isotretinoin and for a period of 5-6 months after treatment because of the risk of dermatitis.

9. Special Patient Groups: In high-risk patients (with diabetes, obesity, alcoholism or disorders of liquid metabolism) undergoing treatment with isotretinoin, more frequent checks of the relevant laboratory parameters will be necessary.

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

Dental problems can occur resulting from dryness of mouth and may increase dental disease, including tooth decay, gum disease, and fungus infections; regular dental appointments are needed and use of sugarless candy or saliva substitute or melting ice in mouth may be necessary to lessen dental problems.

4.5 Interaction with other drugs, other forms of Interactions

Concurrent therapy with isotretinoin and vitamin A must be avoided as symptoms of hypervitaminosis A may be intensified.

Rare cases of benign intracranial hypertension "pseudotumor cerebri" have been reported after isotretinoin and after tetracyclines. Supplementary treatment with tetracyclines should therefore be avoided.

The effect of microdosed progesterone preparations may be diminished by interaction with isotretinoin. Therefore microdosed progesterone preparations should not be used.

4.6 Uses in Pregnancy and Lactation

Isotretinoin is highly teratogenic. It is therefore contraindicated in women who are pregnant or who may become pregnant while undergoing there is an extremely high risk that a deformed infant will result if pregnancy occurs while taking isotretinoin in any amount even for short periods. Potentially all exposed fetuses can be affected. Major human fetal abnormalities related to isotretinoin administration have been documented, including hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent external auditory canals), micropthalmia, cardiovascular abnormalities and cerebellar malformation.

As isotretinoin is highly lipophilic, the passage of the drug in human milk is very likely. Because of the potential for adverse effects, the use of isotretinoin should be avoided in nursing mothers.

It is recommended that the patient use two forms of effective contraception to prevent pregnancy, starting 1 month before initiation of treatment, during treatment, and for 1 month after discontinuation of treatment. Testing serve to remind the patient of the importance of avoiding pregnancy. If pregnancy occurs, patient should be counseled on whether to continue the pregnancy. Isotretinoin therapy startts only on the second or third day of the next normal period.

4.7 Effects on Ability to Drive and operate Machines

None.

4.8 Adverse/ Undesirable/ Side Effects

Most of the adverse reactions of isotretinoin are dose-related. With the recommended dosage, the risk/benefit ratio is generally acceptable considering the severity of the disease.

Incidence more frequent: chelitis (scaling, redness, burning, pain and other signs of inflammation of lips), epistaxis (nosebleeds) and skin infection.

Symptoms Associated with Hypervitaminosis A: The following symptoms are the most

frequently reported: Dryness of the skin, dryness of the mucosae, eg of the lips, the nasal mucosa (epistaxis), the eyes (conjunctivitis, reversible corneal opacities and intolerance to contact lenses).

Skin and Appendages Disorders: Exanthema, pruritus, dermatitis facialis, sweating, pyogenic granuloma, paronychia, nail dystrophy, increased formation of granulation tissue, persistent hair thinning, reversible alopecia, acne fulminans, hirsutism, hyperpigmentation, photosensitivity.

Musculoskeletal System Disorder: Muscle pain, joint pain, hyperostosis and other bone changes, tendinitis.

Psychiatric and Central Nervous System Disorder: Behavioral disorders, depression, headache, increased intracranial pressure, seizures.

Sensory Disorders: Isolated cases of visual disturbances, impaired hearing at certain frequencies, photophobia, dark adaptation disturbances (decreased night vision), lenticular cataract, keratitis.

Gastrointestinal system Disorders: Nausea, inflammatory bowel disease, eg colitis, ileitis and hemorrhage have been reported to occur.

Liver and Biliary System Disorders: Transitory and reversible increases in transaminases, some cases of hepatitis, In many such cases, the changes have been within the normal range and values have returned to baseline levels during treatment. In other cases, however, it has been necessary to reduce the dose or discontinue treatment with Isotretinoin.Respiratory System Disorders: Bronchospasm.

Disorders of the Blood: Decrease in white cell count, red blood cell parameters, increase or decrease in platelet count, elevated sedimentation rate.

Laboratory Findings: Increase in serum triglyceride and cholesterol levels, hyperuricemia. Decreases in HDL have also been observed, particularly at high dosages and in predisposed patients (with a family history of lipid-metabolism disorders, diabetes, obesity or alcoholism). These changes too, are dose-related, and values return to normal on reduction of the dosage or withdrawal of the drug, Every patient should be warned about the possible occurrence of adverse effects.

Resistance Mechanism Disorders: Local or systemic infections due to grampositive

microorganisms (Staphylococus aureus).Miscellaneous Reactions:

- Lymphadenopathy, hematuria, and proteinuria, pancreatitis (especially patients with high serum triglyceride levels (>800 mg) treated with isotretinoin are at risk of developing pancreatitis), vasculitis (eq. Wegener's granulomatosis).

- Bleeding or inflammation of gums; cataracts or corneal opacities.

4.9 Overdose

Signs of hypervitaminosis A could appear in cases of accidental overdose. Evacuation of the stomach may be indicated in the first few hours after overdosage. The symptoms have been abdominal pain, dizziness, intracranial pressure, headache, severe, nausea, vomiting, irritability, itchy skin.

Treatment of overdose:

To decrease absorption – Evacuation of stomach should be considered within 2 hours of ingestion of acute overdose. Medication should be discontinued in patients with symptoms of overdose who were given therapeutic doses.

Monitoring:

- Monitor for increased intracranial pressure.

- Female patients of childbearing potential should have a pregnancy test at time of overdose and 1 month later; if positive, teratogenic risk and continuance of pregnancy should be discussed.

- Blood samples should be collected and isotretinoin and metabolite concentrations determined.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Isotretinoin is absorbed from the gastrointestinal tract. Taking isotretinoin with food increases bioavailability relative to fasting conditions, probably as a result of easier absorption of this highly lipophilic medication.

Isotretinoin is metabolized in liver and possibly in the gut wall. The major identified metabolite in blood and urine is 4-oxo-isotretinoin, other identified metabolites are tretinoin and 4-oxo-tretinoin.

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

5.2 Pharmacokinetic Properties

The exact mechanism of action of isotretinoin is not known. However, isotretinoin reduces sebaceous gland size and inhibits sebaceous gland activity, thereby decreasing sebum secretion.

5.3 Preclinical Safety Data

Not done.

6. Pharmaceutical Particulars

6.1 List of Excipients

Capsule Fill: Beewax White, Butylated Hydroxyanisole, Disodium EDTA, Hydrogenated Vegetable Oil and Soyabean oil.

Capsule Shell: Gelatin, Glycerin, Sorbitol 76% solution (sorbitol special), Purfied Water, Carmosine, Brilliant Blue, Ponceau 4R, Iron Oxide Black and Titanium Dioxide.

6.2 Incompatibilities

None.

6.3 Shelf Life

24 months from date of manufacture.

6.4 Special Precautions for Storage

Store below 30ºc in a dry place. Protect from heat and direct sunlight.

7. Marketing Authorization Holder

MEGA LIFESCIENCES Public Company Limited

384 Moo 4, Soi 6, Bangpoo Industrial Estate,

Pattana 3 Road, Phraeksa, Mueang,

Samutprakarn 10280, Thailand.

8. Marketing Authorization Number:

Thailand: **1A 75/46**

9. Date of first Registration/ Renewal of the Registration

Thailand: **17/03/2003**

10. Date of revision of the text: N/A