

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product :

1.1 Product Name : ACNOTIN 10 and ACNOTIN 20

1.2 Strength : Provided in quality and quantitative composition

1.3 Pharmaceutical Dosage Form : Soft gelatin capsule

2. Quality and Quantitative Composition :

2.1 Qualitative Declaration

2.2 Quantitative Declaration

ACNOTIN 10

Name of ingredient	Specification	Label claim per capsule	Overages per capsule	Quantity per capsule
Active ingredient:				
Isotretinoin	USP Current Edition	10.0000 mg	-	10.0000 mg
Total weight of active ingredients				10.0000 mg
Inactive ingredients:				
Soyabean Oil	EP Current Edition	-	-	119.5760 mg
Hydrogenated Vegetable Oil	USP Current Edition	-	-	20.8000 mg
Beewax White	EP Current Edition	-	-	9.6000 mg
Butylated Hydroxyanisole	EP Current Edition	-	-	0.0224 mg
Disodium EDTA	USP Current Edition	-	-	0.0016 mg
Total weight of inactive ingredients				150.0000 mg
Total fill weight				160.0000 mg
Capsule shell:				
Gelatin	EP Current Edition	-	-	60.7921 mg
Sorbitol Special	USP Current Edition	-	-	22.1062 mg
Glycerin	EP Current Edition	-	-	6.9082 mg
Purified Water	EP Current Edition	-	-	4.2000 mg
Titanium Dioxide	EP Current Edition	-	-	0.5527 mg
Ponceau 4R	In-house specification	-	-	0.0276 mg
Iron Oxide Black	USP Current Edition	-	-	0.0069 mg

Carmoisine	In-house specification	-	-	0.0028 mg
Brilliant Blue	In-house specification	-	-	0.0028 mg
Total shell weight				94.5993 mg
Total capsule weight				254.5993 mg

ACNOTIN 20

Name of ingredient	Specification	Label claim per capsule	Overages per capsule	Quantity per capsule
Active ingredient:				
Isotretinoin	USP Current Edition	20.0000 mg	-	20.0000 mg
Total weight of active ingredients				20.0000 mg
Inactive ingredients:				
Soyabean Oil	EP Current Edition	-	-	239.1520 mg
Hydrogenated Vegetable Oil	USP Current Edition	-	-	41.6000 mg
Beewax White	EP Current Edition	-	-	19.2000 mg
Butylated Hydroxyanisole	EP Current Edition	-	-	0.0448 mg
Disodium EDTA	USP Current Edition	-	-	0.0032 mg
Total weight of inactive ingredients				300.0000 mg
Total fill weight				320.0000 mg
Capsule shell:				
Gelatin	EP Current Edition	-	-	114.9331 mg
Sorbitol Special	USP Current Edition	-	-	41.7938 mg
Glycerin	EP Current Edition	-	-	13.0606 mg
Purified Water	EP Current Edition	-	-	8.1000 mg
Titanium Dioxide	EP Current Edition	-	-	2.8733 mg
Ponceau 4R	In-house specification	-	-	0.0261 mg
Iron Oxide Black	USP Current Edition	-	-	0.0065 mg
Carmoisine	In-house specification	-	-	0.0026 mg
Brilliant Blue	In-house specification	-	-	0.0026 mg
Total shell weight				180.7986 mg
Total capsule weight				500.7986 mg

3. Pharmaceutical Form :

ACNOTIN 10

Pharmaceutical form: Orange colour, oily suspension, filled in 3 minim, oval, purple, opaque soft gelatin shell capsule.

ACNOTIN 20

Pharmaceutical form: Orange colour, oily suspension, filled in 6 minim, oval, opaque purple and opaque white soft gelatin shell capsule.

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.

Acnotin 10/20 should only be prescribed by physicians who are experienced in the use of systemic retinoids, preferably dermatologists, and understand the risk of teratogenicity if Acnotin 10/20 is used during pregnancy.

4.2 Posology and method of administration:

The therapeutic response to isotretinoin and side effects vary according to the individual patient needing individual dose adjustments during therapy. Therapy should be started with 0.5 mg/kg daily. During the initial period of isotretinoin therapy, transient exacerbation of acne can occur. After about 4 weeks, dosage for maintenance treatment should be adjusted to recommended maintenance dose range of 0.1 – 1.0 mg/kg per day to meet individual needs. Treatment usually lasts a total of 16 weeks. Patients with very severe disease or with truncal acne may require higher daily doses up to 2.0 mg/kg.

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 capsule should be taken with meals, low doses once daily, and higher amounts as a single dose or in several doses spread over the day. Concurrent administration of other

keratolytic or exfoliative antiacne agents is not indicated, nor is concurrent radiotherapy with ultraviolet light indicated. Patients should avoid exposure to the sun.

Patient with severe renal insufficiency should be started at a lower dose (e.g. 10 mg/day) and afterwards individually adjusted according to tolerance.

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 should be avoided to prevent accidental exposure of the developed fetus of a pregnant patient who may receive such blood.
3. Pregnancy, Nursing Mothers

Isotretinoin is highly teratogenic. It is therefore contraindicated not only in women who are pregnant or who may become pregnant while undergoing treatment but in all women of childbearing potential. 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.

Acnotin 10/20 is contraindicated in women of childbearing potential unless the female patient meets all the following conditions:

- She has severe acne resistant to standard therapies.
- She is reliable in understanding and carrying out instructions.
- She is capable of complying with mandatory effective contraceptive measures.
- She is informed by her physician of the hazards of becoming pregnant during and 1 month after treatment with Acnotin 10/20.
- She is warned of the possibility of contraceptive failure. Monthly pregnancy testing is commended.
- She uses effective contraception without any interruption for 1 month before beginning Acnotin 10/20 therapy, during therapy and for 1 month following discontinuation of therapy. It is recommended to use two forms of effective contraception to prevent pregnancy.
- She starts Acnotin 10/20 therapy only on the 2nd or 3rd day of the next normal menstrual period.
- In the event of relapse treatment she must also use the same uninterrupted and

effective contraceptive measures 1 month prior to, during and for 1 month after Acnotin 10/20 therapy and the same reliable pregnancy evaluations should be followed.

- Even female patients who normally do not apply 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 contraception while taking Acnotin 10/20 following the above guidelines.
- Should pregnancy occur in spite of these precautions during treatment with Acnotin 10/20 or in the month following, there is a great risk of very severe malformations of the fetus (involving in particular the central nervous system, the heart and the large blood vessels). 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), microphthalmia, cardiovascular abnormalities, facial dysmorphism, thymus gland abnormalities. There is also an increased risk of spontaneous abortion. If pregnancy does occur, the physician and patients should discuss the advisability of continuing the pregnancy.
- She confirms that she has understood the precautions.
- 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 during pregnancy.

4.4 Special warning 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. Both female and male patients should be given a copy of the Patient Information Brochure.
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 start of therapy, and also at end of the 3- to 4-month treatment period). Blood glucose levels should be monitored in diabetic patients.
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 of necessary.

4. Patients experiencing visual problems should be referred for an expert ophthalmological examination and withdrawal of Acnotin 10/20 should be considered. Visual problem should be carefully monitored. Vision problems that can occur include photophobia, blurred vision or dryness of the eyes. In some patients onset of decreased night vision may be sudden, and patients should be advised of this potential problem and warned to be cautious when driving or operating any machinery at night. Due to the possible occurrence of keratitis, patients with dry eyes should be monitored. Wearing contact lenses may be uncomfortable.
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, contraceptive containing an androgen progestational substance, such as one derived from 19-nortestosterone (norgestrel), particularly in the presence of gynecological problems should be avoided.
7. Dermabrasion should be avoided in patients on isotretinoin and for a period of 5 – 6 months 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 6 months after treatment because of the risk of dermatitis or possibility of scarring.
9. Avoid prolonged exposure to sunlight.
10. Special patient groups: In high-risk patients (with diabetes, obesity, alcoholism or disorders of lipid metabolism) undergoing treatment with isotretinoin, more frequent checks of serum lipids and/or blood glucose 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. Avoid prolonged exposure to sunlight.

4.5 Undesirable 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: cheilitis (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, photoallergic reaction, skin fragility.

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

Psychiatric and Central Nervous System Disorders: 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, e.g. 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 Mechanisms Disorders: Local or systemic infections due to gram-positive microorganisms (*Staphylococcus 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 (eg. Wegener's granulomatosis).
- Bleeding or inflammation of gums; cataracts or corneal opacities.

4.6 Interactions with other medicaments:

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 not be used during Acnotin 10/20 therapy.

4.7 Overdose and special antidotes:

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 sample should be collected and isotretinoin and metabolite concentrations

determined.

5. Pharmacological Properties:

5.1 Pharmacodynamic Properties:

The exact mechanism of action of isotretinoin is not known in detail. However, the pharmacological profile of isotretinoin suggest that it acts by reducing sebaceous gland size and inhibits sebaceous gland activity, thereby decreasing sebum secretion, Further more a dermal anti-inflammatory effect of isotretinoin has been established.

5.2 Pharmacokinetic Properties:

Time related blood concentrations can be predicted on the basis of linear pharmacokinetics.

Absorption: Peak plasma concentrations (C_{max}) of approximately 250 ng/ml have been achieved in healthy volunteers and in patients with cystic acne one to four hours (T_{max}) after administration of 80-100 mg isotretinoin. Taking isotretinoin with food increases bioavailability pu to two fold relative to fasting conditions, probably as a result of easier absorption of this highly lipophilic medication. Furthemore, there was an overall decrease in fluctuations in systemic availability when isotretinoin is ingested with food.

Distribution: Isotretinoin is extensively bound to plasma proteins (99.9%), with the result that the free active fraction of the drug is less than 0.1% of the total over a wide range of the therapeutic concentrations. Albumin appears to be the major binding protein. The volume of distribution of isotretinoin is not known in man since it is not available as an intravenous preparation. Isotretinoin crosses the placental barrier in amounts that lead to congenital deformities. Owing to its liphophilicity, there is a high probability that isotretinoin is excreted into the breast milk. It is therefore contraindicated in nursing mothers.

Metabolism: The major blood metabolite of isotretinoin is 4-oxo-isotretinoin, which is rapidly formed following oral administration of the drug. Isotretinoin also isomerizes in vivo via an alternative metabolic pathway to tretinoin (all-trans retinoic acid). Glucuronidation of the metabolites has not been conclusively demonstrated in man but is strongly suggested by animal studies. Investigations in human and the dog point to an enterohepatic recirculation of isotretinoin, which would contribute to the observed interindividual variability in plasma concentrations.

Elimination: Isotretinoin appears to be eliminated almost exclusively by hepatic metabolism and biliary excretion. Following oral administration of isotretinoin, the elimination half-life

of unchanged drug ranged from 7-39 hours (mean: approximately 20 hours) in both healthy volunteers and patients with cystic acne. The mean elimination half-life of 4-oxo-isotretinoin in patients with cystic acne is slightly longer (25 hours, range: 17-50 hours) than that of the parent drug.

Pharmacokinetics in special clinical situations: Since isotretinoin is contraindicated in patients with renal or hepatic impairment, there is no information on the pharmacokinetics of the drug in this population.

5.3 Preclinical Safety Data:

Not applicable.

6. Pharmaceutical Particulars :

6.1 List of excipients:

Inactive: Soyabean Oil, Hydrogenated Vegetable Oil, Beewax White, Butylated Hydroxyanisole, Disodium EDTA, Gelatin, Sorbitol Special, Glycerin, Purified Water, Titanium Dioxide, Ponceau 4R, Iron Oxide Black, Carmoisine & Brilliant Blue

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

Two years from manufacture date.

6.4 Special precautions for storage:

Store below 25°C in a dry place, away from direct sunlight.

6.5 Nature and contents of container :

Aluminium foil:	Printed aluminium foil
Outer carton:	Printed cardboard carton
Insert:	Wood free paper

7. Marketing Authorization Holder :

MEGA LIFESCIENCES Public Company Limited

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8. Marketing Authorization Numbers: -

9. Date of first authorization / renewal of the authorization: -

10. Date of revision of the text: -