For submit in Malaysia
Artwork of insert **"ACNOTIN 10 & 20"** HLM (PCL) code ***RI-I022-H14-00-10***
Size : 195 x 290 mm *(F-I022-H14-D7, F-I023-H14-D7)*
(page 1/2)

195 mm

36.25 mm

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290 mm

For the use of a registered medical practitioner or a pharmacist or a hospital

ACNOTIN 10 / ACNOTIN 20

(Isotretinoin Capsules 10 mg) **(Isotretinoin Capsules 20 mg)**

PRODUCT DESCRIPTION
Acnotin 10
Orange color oily suspension filled in oval, opaque purple color soft gelatin capsule
Acnotin 20
Orange color oily suspension filled in oval, opaque purple and white color soft gelatin capsule

COMPOSITION

Acnotin 10	**Acnotin 20**
Each softgel capsule contains :	**Each softgel capsule contains :**
Isotretinoin.....10 mg	Isotretinoin..... 20 mg

Route of administration: Oral

DESCRIPTION
Isotretinoin is 13-cis retinoic acid. It is a synthetic stereoisomer of all-trans retinoic acid (tretinoin). It is a yellow-orange to orange crystalline powder with a molecular weight of 300.44.

INDICATIONS
Acnotin 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.

CLINICAL PHARMACOLOGY
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.
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 biliary excretion.

CONTRAINDICATIONS
Acnotin is contraindicated in women who are pregnant or breastfeeding (see section Pregnancy & Lactation).
Acnotin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section Warning).
Acnotin is also contraindicated in patients with hypersensitivity to Isotretinoin or to any of the excipients. Acnotin contains soya oil, partially hydrogenated soya oil, and hydrogenated soya oil. Therefore, Acnotin is contraindicated in patients allergic to peanut or soya.
Acnotin is also contraindicated in patients
– With hepatic insufficiency
– With excessively elevated blood lipid values
– With hypervitaminosis A
– Receiving concomitant treatment with tetracyclines (see section Interactions)

PREGNANCY & LACTATION
Pregnancy:
Pregnancy is an absolute contraindication to treatment with isotretinoin. Women of childbearing potential have to use effective contraception during and up to one month after treatment. If pregnancy does occur in spite of these precautions during treatment with Isotretinoin or in the month following, there is a great risk of very severe and serious malformation of the foetus.
The foetal malformations associated with exposure to isotretinoin include central nervous system abnormalities (hydrocephalus, cerebellar malformation/ abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.
If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.
Isotretinoin is highly lipophilic, therefore the passage of isotretinoin into human milk is very likely. Due to the potential for adverse effects in the child exposed via mothers' milk, Isotretinoin is contraindicated during breast-feeding.

WARNINGS AND PRECAUTIONS

Teratogenic effects
- Acnotin is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects.

Acnotin is strictly contraindicated in:
- Pregnant women.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met.

Acnotin is TERATOGENIC.
There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking oral Acnotin in any amount even for short periods. Potentially all exposed fetuses can be affected.
Acnotin is contraindicated in women of child-bearing potential unless the female patient meets all the conditions of the Pregnancy Prevention Programme.
The pregnancy prevention information should be given to the patients both orally and in writing.
Pregnancy Prevention Programme
This medicinal product is TERATOGENIC
Acnotin is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:
- Acnotin is indicated for the treatment of severe forms of acne (nodular or conglobate acne, or acne at risk of permanent scarring) and acne which has failed to respond to standard therapies with systemic antibacterials and topical therapy. (See Section Indication).
- The potential for pregnancy must be assessed for all female patients.
- She understands the teratogenic risk.
- She understands the need for rigorous follow-up on a monthly basis.
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the entire duration of treatment and for 1 month after the end of treatment.
  At least one highly effective method of contraception (i.e. a user- independent form) or two complementary user-dependent forms of contraception should be used.
- Individual circumstances should be evaluated in each case, when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.
- Even if she has amenorrhea she must follow all of the advice on effective contraception.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy or if she might be pregnant.
- She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and 1 month after stopping treatment.
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of Acnotin.

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.
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 Acnotin, following the above guidelines.
The prescriber must ensure that:
- The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.
- The patient understands that she must consistently and correctly use one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception, for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment.
- Negative pregnancy test results have been obtained before, during and 1 month after the end of treatment. The dates and results of pregnancy tests should be documented.

If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.
If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the foetus. This risk persists until the product has been completely eliminated, which is within one month following the end of treatment.
Contraception:
Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. If the prescribing physician is not in a position to provide such information the patient should be referred to the relevant healthcare professional.
As a minimum requirement, female patients of childbearing potential must use at least one highly effective method of contraception (i.e. a user-independent form), or two complementary user-dependent forms of contraception. Contraception should be used for at least 1 month prior to starting treatment, throughout treatment and continue for at least 1 month after stopping treatment with isotretinoin, even in patients with amenorrhea.
Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.
Pregnancy testing:
Prior to starting therapy:
At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a medically supervised pregnancy test. This test should ensure the patient is not pregnant when she starts treatment with Acnotin.
Follow-up visits:
Follow-up visits should be arranged at regular intervals, ideally monthly.
Follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.
End of treatment:
One month after stopping treatment, women should undergo a final pregnancy test.
Prescribing and dispensing restrictions:
For women of childbearing potential, the prescription duration of Acnotin should ideally be limited to 30 days in order to support regular follow up, including pregnancy testing and monitoring. Ideally, pregnancy testing, issuing a prescription and dispensing of Acnotin should occur on the same day.
This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patient is not pregnant before receiving the next cycle of medication.
Male patients:
The available data suggest that the level of maternal exposure from the semen of the patients receiving Acnotin, is not of a sufficient magnitude to be associated with the teratogenic effects of Acnotin. Male patients should be reminded that they must not share their medication with anyone, particularly females.
Additional precautions:
Patients should be instructed never to give this medicinal product to another person, and to return any unused capsules to their pharmacist at the end of treatment.
Patients should not donate blood during therapy and for 1 month following discontinuation of Acnotin 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 Acnotin, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.
For physicians:
– Physician's Checklist/ Acknowledgement Form for Prescribing to Female Patients
For patients:
- Patient Reminder Card
For pharmacists:
– Pharmacist's Checklist- Guidance for Dispensing Acnotin
Skin and subcutaneous tissues disorders
Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually within 7-10 days, and usually does not require dose adjustment.
Exposure to intense sunlight or to UV rays should be avoided. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used. Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on Acnotin and for a period of 5–6 months after the end of treatment because of the risk of hypertrophic scarring in atypical areas and more rarely hyper- or hypopigmentation in treated areas. Wax epilation should be avoided in patients on Acnotin

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therapy and at least for a period of 6 months after treatment due to the possibility of epidermal stripping, scarring or dermatitis.
Concurrent administration of Acnotin with topical keratolytic or exfoliative antiacne 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 Acnotin 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 Acnotin use. These events may be serious and result in death, life-threatening events, hospitalisation, or disability. Patients should be monitored closely for severe skin reactions and discontinuation of Acnotin should be considered if warranted.

Eye disorders
Dry eyes, corneal opacities, decreased night vision, keratitis, blepharitis and conjunctivitis resolve after discontinuation of therapy. Cases of dry eyes not resolving after discontinuation of therapy have been reported. 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 occurred during Acnotin therapy and in rare instances has persisted after discontinuation of therapy. 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 any vehicle at night. Visual problems should be carefully monitored.

Musculo-skeletal and connective tissue disorders
Sacroiliitis has been reported in patients exposed to Acnotin. To differentiate sacroiliitis from other causes of back pain, in patients with clinical signs of sacroiliitis, further evaluation may be needed including imaging modalities such as MRI. In cases reported post-marketing, sacroiliitis improved after discontinuation of Acnotin and appropriate treatment.
Myalgia, arthralgia and increased serum creatine phosphokinase may occur and may be associated with reduced tolerance to vigorous exercise.
Bone changes, including premature epiphyseal closure, hyperostosis and calcifications of tendons and ligaments have occurred after several years of administration at 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. Therefore, a careful evaluation of the risk/benefit ratio should be carried out in every patient.

Benign intracranial hypertension
Rare cases of benign intracranial hypertension "pseudotumor cerebri" have been reported, some of which involved concomitant use of tetracyclines. Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilledema. Patients who develop benign intracranial hypertension should discontinue Acnotin immediately.
Therefore, concomitant treatment with tetracyclines should be avoided.

Hepatobiliary disorders
Liver function or enzymes should be checked before and 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, when transaminase level exceed the normal levels, reduction of the dose or discontinuation of treatment may be necessary.

Lipid Metabolism
Serum lipids (fasting value) should also be checked, 1 month after the start of therapy, and subsequently at 3 months intervals unless more frequent monitoring is clinically indicated. The serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment. The changes in serum lipids may also resolve in response to dietary measures.
It is recommended to control clinically significant serum triglyceride elevations, since levels in excess of 800 mg/dl or 9 mmol/l are sometimes associated with acute pancreatitis, which is known to be potentially fatal. Hence, Acnotin should be discontinued if uncontrolled hypertriglyceridemia or symptoms of pancreatitis occur.

Gastrointestinal disorders
Acnotin has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing severe (haemorrhagic) diarrhoea should discontinue Acnotin immediately.

Allergic reactions
Anaphylactic reactions have been rarely reported and only 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 Acnotin, 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 Acnotin therapy.

Psychiatric symptoms:
Depression, depression aggravated, anxiety and mood alterations, have been reported in patients treated with systemic retinoids. Particular care should be taken in patients with a history of depression. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary.
Awareness by family or friends may be useful to detect mental health deterioration.
Suicidal ideation, suicide attempts and suicide have been reported in patients treated with Acnotin.

ADVERSE REACTIONS

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. Cases of sacroiliitis have been observed in patients treated with isotretinoin (see section Warnings and Precautions)

Renal and urinary disorders: Cases of urethritis have been reported.

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, hyperuricmia. 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 gram-positive 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 (eg. Wegener's granulomatosis).
– Bleeding or inflammation of gums; cataracts or corneal opacities.

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.

OVERDOSAGE

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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

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.

DOSAGE & ADMINISTRATION

The usual adult and adolescent dose is 0.5 to 1 mg/kg of body weight per day (in two divided doses) for 16 to 24 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.

Concurrent Topical Therapy: Concurrent administration of other keratolytic or exfoliative antiacne agents is not indicated, nor is concurrent radiation therapy with ultraviolet light indicated. Patients should avoid exposure to the sun. Adjuvant therapy with mild topical antiacne drugs may be given, as required.

STORAGE

Store below 30ºC in a dry place. Protect from heat and light.

PRESENTATION

Acnotin 10 – Strip of 10's, 3 strips per box.
Acnotin 20 – Strip of 10's, 3 strips per box.

Manufactured by :
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Artwork Check / Layout Check			
PC TEAM		**PRODUCTION**	**RA**
Provide by : *Nuthchamon* Date : *12-Jun-26* - Revise as comment for submit. Department head approved : …… Date : …… Final artwork from RA/Customer approved : …… Date : ……	PC Check ☐ Pass : …… …… …… ☐ Not Pass : …… …… ……	Production Check 1 : ☐ Pass : …… ☐ Not pass : …… Production Check 2 : ☐ Pass : …… ☐ Not pass : …… Production Department Head : ☐ Pass : …… ☐ Not pass : ……	Need to send for customer approval ☐ Yes, please send …… …… ☐ Not require …… ……

Specification
Offset Printing Paper 60 gsm
Verified by : ……