A-CNOTREN® ISOTRETINOIN

PATIENT INFORMATION LEAFLET

1. DEFINITION OF THE MEDICINAL PRODUCT

1.1 NAME: A-CNOTREN

1.2 COMPOSITION:

Active substance: Isotretinoin

Excipients: Refined soya oil, yellow beeswax, hydrogenated soya oil, partially hydrogenated vegetable oil.

Composition of empty capsule: Gelatin, glycerol 99,5 %, titanium dioxide E 171 CI 77891, Iron oxide (red) E 172, CI 77491, Iron oxide (yellow) E 172 CI 77492

1.3 PHARMACEUTICAL FORM: Capsule, soft.

1.4 CONTENT: Each soft capsule contains 20 mg isotretinoin.

1.5 DESCRIPTION - PACKAGE:

Cardboard box containing 30 red – orange capsules packaged in 3 blisters of 10 cap (PVC/PE/PVDC/aluminium foil) each, on which the expiry date and lot number of the product are printed. Accompanied by instructions for use.

1.6 PHARMACOTHERAPEUTIC CATEGORY:

Preparations against acne for systematic use.

1.7 MARKETING AUTHORIZATION HOLDER:

Pharmathen S.A.: 6, Dervenakion Str., Pallini, GR 153 51 Attiki, Tel.: 210.6665.067, Fax: 210.6666749

1.8 MANUFACTURER(S):

- GAP, 46 Agisilaou str., 173 41 Ag. Dimitrios, Athens, Greece.

2. THINGS THE PATIENT SHOULD KNOW ABOUT THE MEDICINE:

2.1 GENERAL INFORMATION:

The medicine contains the active substance isotretinoin, which is a derivative of vitamin A and belongs in the category of retinoids. The later are usually used for the treatment of skin diseases.

Treatment with A-Cnotren should take place only under the supervision of a medical dermatologist with experience in the treatment of severe acne and full understanding of the risks that lie behind treatment with isotretinoin. The dermatologist should also be well aware of the danger of teratogenesis that relates to treatment with isotretinoin.

2.2 INDICATIONS:

Severe forms of acne (such as nodose or swarming acne or acne presenting a risk of permanent scars) that resist to adequate therapeutic circles of usual treatment with systematically administered antibiotics and local treatment.

2.3 CONTRAINDICATIONS:

The medicine is contraindicated in the following cases:

- If you are pregnant or breastfeeding.
- If there is a possibility for you to get pregnant.
- If you suffer from hepatic failure.
- If your blood lipid levels are too high (cholesterol, triglycerides).
- If your organism's vitamin A levels are too high (hypervitaminosis A).
- If you present hypersensitivity (allergy) to isotretinoin or any other ingredient of A-Cnotren.
- If you receive tetracyclines (a type of antibiotic).

2.4 SPECIAL PRECAUTIONS AND WARNINGS FOR USE:

2.4.1 GENERAL:

- If you have a history of high blood lipid levels (triglycerides or cholesterol), please notify your doctor. Your doctor shall ask you to perform certain blood examinations so as to monitor your blood values before, during and after treatment with A-Cnotren.
- A-Cnotren may increase the levels of hepatic enzymes. Your doctor shall ask you to perform regular blood examinations before and during treatment with A-Cnotren, so as to monitor your liver values. If the levels of your hepatic enzymes remain high, your doctor may reduce the dose you receive or he/ she may ask you to discontinue treatment with the medicine.
- If you suffer from diabetes mellitus, the medicine may cause increase in your blood sugar levels. Your doctor may frequently monitor your blood sugar values during treatment.
- If you are overweight or suffer from any disorder of lipid metabolism or consume extreme amounts of alcohol, your blood lipid and sugar levels may increase. In these cases, your doctor may decide that you should perform more frequent blood examinations.
- Rare occasions of depression and psychotic symptoms and very rare cases of suicide attempt and suicide have been reported. If you have any kind of psychic problems or if you notice any signs of depression while you receive A-Cnotren, please notify your doctor. He/ she may refer you, if required, for proper treatment. Termination of A-Cnotren treatment may not be adequate for the improvement of symptoms and you may require further psychiatric or psychological evaluation.
- If you present any allergic reactions (skin redness, itch) or any anaphylactic reaction, please notify your doctor, who might ask you to discontinue treatment with A-Cnotren.
- In case of persistent headache, nausea, vomit and blur vision or severe (hemorrhagic) diarrhea, please discontinue treatment immediately and contact your doctor as soon as possible.
- Treatment with A-Cnotren may affect your night vision. During treatment with A-Cnotren, you may develop eye dryness or vision problems. These signs rarely persist after treatment. In case they are noted, please notify your doctor immediately, so as to undergo an ophthalmologic examination. If you drive or use machines at night, always be careful, since these vision changes may appear rather suddenly. If you wear contact lenses and your eyes become dry, you may need to wear eyeglasses during treatment with A-Cnotren.
- Your skin may be more sensitive to sunlight during treatment with A-Cnotren. Avoid extreme exposure to sun and do not use artificial tanning methods (solarium). Before your exposure to sunlight, use a sun care product with high protection index (SPF at least 15).
- Treatment with A-Cnotren may cause your skin to become more fragile. Intense dermoabrasion (removal of hard skin or scars), as well as wax depilation should be avoided during treatment and for a period of at least six months after treatment due to the probability of scars or skin irritation.
- Since during treatment with A-Cnotren you may present dryness of the skin and/ or of the lips, you may use a hydration ointment or cream, as well as an emollient product for the lips.
- Muscular pain and pain at the joints has been noted during treatment with A-Cnotren, Therefore, you should reduce intense physical activity during treatment with A-Cnotren.
- If your kidneys present malfunction, please notify your doctor. Your treatment should initiate at a much lower dose.
- If you suffer from any other disease, please notify your doctor.
- Do not donate blood while receiving A-Cnotren and up to one month after the end of treatment. If your blood is transfused to a pregnant woman, her baby may be born with severe congenital abnormalities (birth defects).

2.4.2 ELDERLY PATIENTS: No special warnings regarding elderly patients.

2.4.3 PREGNANCY:

Pregnant womenThe medicine is contraindicated during pregnancy.

Important: The medicine is teratogenic, meaning, it may harm the fetus.

Increased risk of miscarriage.

You should not receive A-Cnotren if you are pregnant or if there is a possibility for you to get pregnant during treatment and for one month after the end of treatment.

If you are a female patient at a reproductive age, you can receive the medicine only if:

- You suffer from severe acne (such as nodose or swarming acne or acne presenting a risk of permanent scars) that resist to adequate therapeutic circles of usual treatment with systematically administered antibiotics and local treatment.
- Your doctor has explained the teratogenesis risk that relates to isotretinoin and you understand why you should avoid pregnancy, as well as the methods of avoiding it.
- You have discussed with your doctor the use of effective contraception methods. Your doctor shall inform you about pregnancy avoidance and he/ she shall give you a leaflet relating to contraception, where several methods are being explained. He/ she may also refer you to an expert for advice on contraception.
- You agree to use at least one and preferably two effective contraception methods for one month before A-Cnotren treatment initiation, during the whole treatment and for one month after treatment termination. Prior to treatment initiation, your doctor shall ask you to undergo a pregnancy test that should be negative.
- You are using contraception even if you have no menses or even if you have no sexual contacts at the moment, unless your doctor decides that something like that is not necessary.
- You understand and accept the necessity of being monitored on a monthly basis, as well as of possibly performing additional pregnancy tests, according to your doctor's judgment. Then, you shall perform a pregnancy test 5 weeks after the termination of A-Cnotren treatment. You should not stay pregnant during the whole treatment and for one month after treatment termination.
- Your doctor may ask you or you guardian to sign an informed consent form where you shall verify that you have been informed regarding the risks that relate to treatment with A-Cnotren and that you accept all necessary precaution measures.

If you get pregnant during treatment or within one month after A-Cnotren treatment termination, immediately discontinue receiving the medicine and notify your doctor, who may refer you to an expert for evaluation and consulting.

Written information regarding the in question matter is available by your doctor. If you have not received the documents, please contact your doctor.

For women at a reproductive age, prescriptions are limited to 30 days of treatment. Treatment continuation requires a new prescription, while each prescription is valid for only seven days.

Male patients:

Use of A-Cnotren does not affect fertility and childes of male patients. There is no limitation regarding the medicine's distribution to male patients. You should always remember not to give the medicine to anyone else, especially women.

2.4.4 LACTATION

You should not receive A-Cnotren if you are breast-feeding since isotretinoin may possibly pass in your milk and harm your baby.

2.4.5 CHILDREN

Isotretinoin is not indicated for the treatment of pre-pubertal acne and is not recommended in patients under 12.

2.4.6 EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES

Your night vision may reduce during treatment. This may occur suddenly. In rare occasions, this reduction persists after treatment. You should also be careful while driving or using machines.

2.4.7 SPECIAL WARNINGS FOR EXCIPIENTS

You should not receive the medicine if you know you are allergic to any of its ingredients.

2.5 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS OR OTHER FORMS OF INTERACTION

Please, notify your doctor or pharmacist in case you receive or have recently received any other medicine, even those distributed without a prescription, including herbal products.

During treatment with A-Cnotren, do not receive tetracyclines.

During treatment with A-Cnotren, do not receive nutrition complements containing vitamin A. The concomitant use of both medicines may increase the risk of undesirable effects.

Avoid the use of ointments and/ or topical keratolytic factors, unless your doctor has recommended them.

2.6 POSOLOGY AND METHOD OF ADMINISTRATION

Always receive the medicine strictly according to your doctor's instructions. If you have any doubts, ask you doctor or pharmacist.

The capsules should be received with food, once or twice daily. Swallow them intact without chewing or sucking them.

The usual initial dose is 0,5 mg per body weight kg daily (0,5 mg/kg/day). After a few weeks, your doctor may re-adjust your dose. This shall depend on the course of your treatment. For most patients, the dose varies between 0,5 and 1,0 mg/kg/day. If you have the impression that the medicine's action is either too strong or too weak, notify your doctor or pharmacist.

If you present severe problems with your kidneys, treatment with A-Cnotren should initiate at a lower dose, p.e, 10 mg/day and then, it should increase up to the maximum tolerance dose.

If you cannot tolerate the recommended dose, your doctor may ask you to continue treatment at a lower dose: in such a case, your treatment shall last longer while the risk of relapse shall be greater.

In some cases, acne may deteriorate during the first weeks of treatment. Improvement is anticipated with treatment continuation.

A therapeutic circle usually lasts from 16 to 24 weeks. Improvement of the acne may be noted for a period of up to 8 weeks after the treatment's termination. For this reason, no new treatment circle should begin at least before the end of the 8-week period. Most patients need only one treatment circle.

At the end of the treatment, keep all unused capsules only if indicated by your doctor. Always remember that this medicine is only for you. Only a doctor may prescribe the medicine. Never give your medicine to other people. It may cause them harm, even if their symptoms are the same as yours.

2.7 OVERDOSE - TREATMENT

In case you receive an extremely great number of capsules or in case someone else accidentally receives your medicine, immediately contact your doctor, your pharmacist or the nearest hospital.

Athens Poisoning Center: 210.7793777

2.8 UNDESIRABLE EFFECTS

As with all medicines, treatment with isotretinoin may cause undesirable effects. These undesirable effects usually attenuate with treatment continuation. Your doctor may help you with their treatment.

Sever undesirable effects:

The following undesirable effects have rarely been reported in patients receiving isotretinoin:

During the use of isotretinoin and in rare occasions, patients may present a bad mood. Rare cases of depression and very rarely, cases of suicide and suicide attempt have been reported. Very rarely, there have been reports of patients who presented abnormal behavior and psychotic disorder. Given the fact that depression and other psychiatric disorders may be hereditary, chronic diseases, notify your doctor in case you present psychic problems of any kind or if you note signs of depression during treatment with isotretinoin. The discontinuation of isotretinoin's treatment may not be adequate for the improvement of symptoms and you may possibly need further psychiatric or psychological evaluation.

The following undesirable effects have rarely and very rarely been reported in patients receiving isotretinoin:

Feeling of chest gripe and difficulty in breathing (especially if you suffer from asthma) accompanied by skin exanthema and itching may mean that you are presenting allergic reactions to the medicine. In case you present allergic reaction (hypersensitivity), you should immediately discontinue treatment and consult your doctor.

In very rare occasions, patients receiving isotretinoin have a feeling of extreme thirst, need to go to the bathroom many times and present increased levels of blood sugar, a sign indicative of development of diabetes. For this reason, you doctor may monitor your blood sugar levels more frequently during treatment.

During the concomitant use of isotretinoin and several antibiotics (tetracyclines), benign intracranial tension, spasm and somnolence have very rarely been noted. The occurrence of any persistent headache along with nausea, vomit and blurred vision (caused by edema of the optic papilla) may possible mean that you have presented benign intracranial tension. Stop receiving isotretinoin as soon as possible and contact your doctor.

In case you notice intense abdominal pain with or without severe hemorrhagic diarrhea, nausea and vomit, stop receiving isotretinoin as soon as possible and contact your doctor. There are very rare reports of patients who presented gastrointestinal disorders, such as pancreatitis, gastrointestinal hemorrhage, colitis, ileitis and inflammatory disease of the bowel.

In case your skin or eyes turn yellow and you experience fatigue, you might have developed hepatitis. Even thought such a sign has very rarely been noted in patients receiving isotretinoin, discontinue the medicine as soon as possible and contact your doctor.

In very rare occasions, patients present kidney inflammation. They feel extremely tired, cannot urinate and their eyelids are swollen. In such a case, stop receiving the medicine and contact your doctor.

Non severe undesirable effects:

The following undesirable effects have very commonly or commonly been reported in patients receiving isotretinoin:

You should expect dryness of the skin and especially of the lips and face. You may develop inflammation of the pharynx or of the skin, cracking of the skin or of the lips, exanthema, mild itching and slight peeling. You may alleviate dryness by using a good hydration cream on a regular basis from the beginning of the treatment. You should expect possible occurrence of dryness and formation of a "crust" on the inside of your nose, something that can cause mild hemorrhage by the nose. Application of a small amount of hydration cream is indicated.

Also, the use of an ointment on the inside of the nose is indicated and can be very helpful. You may also feel your eyes dried and slightly irritated. Ask your pharmacist to recommend the appropriate eye drops for alleviation of the dryness. Very rarely, patients who wear contact lenses may need to wear eyeglasses during treatment, due to eye dryness.

All the aforementioned undesirable effects, including skin and mucous membrane dryness, as well as irritation of the eyes, eyelids or conjunctiva are similar to those noted with the use of extreme amounts of vitamin A. Such undesirable effects are usually reversible after the treatment's discontinuation.

Your skin, especially on your face, may become more fragile and redder than it usually is. During treatment and for a time period of at least 6 months after, intense dermoabrasion and depilation should be avoided, due to the possibility of scars or skin irritation.

Back pain has very commonly been reported in patients receiving isotretinoin. This symptom is reversible after the treatment's discontinuation. During treatment with isotretinoin, muscular and articular pain has very commonly been reported. For this reason, you should limit intense physical activity during treatment.

Anemia and increased sedimentation rate occur very commonly. Additionally, reduced levels of blood thrombocytes have been noted, something that causes deceleration of the blood's coagulation process. Therefore, you may present bruises or hemorrhage more easily. In some cases, isotretinoin may cause abnormalities on the levels of certain substances, such as proteins and blood cells that are excreted via the urine. Notify your doctor in case you notice any change in your urine.

The occurrence of abnormal levels of certain metabolism products of the organism in the blood has also been commonly reported in patients, such as increased levels of blood sugar or hepatic enzymes.

You doctor may ask you to undergo certain blood examinations so as to monitor your liver and blood values before, during and after treatment.

Given the fact that isotretinoin may very often cause abnormalities on the levels of certain fatty substances (triglycerides, high density lipoproteins and some times, cholesterol) in the blood of some patients, it is preferred not to consume alcoholic beverages during treatment or at least, reduce the amount you usually consume. If during treatment your doctor ascertains that your triglycerides' levels are high, you might need to reduce isotretinoin's dose and follow a low fat diet.

The following undesirable effects have very rarely or rarely been reported in patients receiving isotretinoin:

In some cases, deterioration of acne may be noted during the first weeks of treatment. In very rare cases, your skin may present inflammation and swelling. However, acne and other symptoms are expected to improve with treatment continuation.

In very rare occasions, you may present extreme perspiration and itching. During exposure to sunlight, you may, very rarely, present increased photosensitivity. For this reason, you should always be protected. Prior to exposure to sunlight, apply a sun care product with a high protection index (SPF of at least 15) on the areas that are exposed to sunlight, especially if it is intense. Avoid exposure to ultraviolet radiation (UV).

You may also, very rarely, present local bacterial infections, such as infection of the tissue around the base of the nails, edemas with pus or inflammation of the blood vessels, changes in your hair, changes in your nails, thickening of scars after surgical operations, increase in the skin's pigments on the face and increased growth of hair on your body.

Most of isotretinoin's undesirable effects shall disappear when you discontinue treatment.

You may notice some changes in your hair (loss or rarely, increase) after a small period of taking the medicine. This is usually transient while persistent weakening of the hair is rare. Your hair is expected to return to its normal condition after the end of treatment.

Very rarely, you might develop dryness of the pharynx that may cause your voice to become huskier.

In very rare occasions, some patients may present hearing damage.

Reduction in the blood's white cells has some times been reported and very rarely, dilatation of the lymph glands. Therefore, patients presenting such symptoms have increased probabilities of being infected by bacterial infections.

In very rare occasions, your night vision may be affected by this medicine and you may develop sight problems that rarely persist after treatment. Also, some patients have difficulty in discerning colors while you may need sunglasses in order to protect your eyes from intense sunlight. In such a case, immediately notify your doctor, so as to monitor your vision. These changes may be noted rather suddenly so always be careful while driving or using machines at night.

In very rare occasions, patients have developed other eye problems (vision disorders), such as blurred vision, blurring of the cornea, keratitis and cataract. Notify your doctor as soon as possible in case you notice any effect of the medicine on your vision.

Furthermore, in very rare occasions, possible development of arthritis, disorders of the bones (including growth delay, exostoses and osteal density alterations) and calcifications of the soft tissues while sometimes pain of the tendons and abnormal levels of muscular rebuild products in your blood when you exercise intensively during treatment have been reported. All these undesirable effects are reversible after the medicine's discontinuation. Premature discontinuation of bone growth may be noted if not previously completed.

In case you notice side effects that are not mentioned in the present leaflet, notify your doctor.

If you are concerned about these or any other undesirable effects, consult your doctor.

2.9 THINGS THE PATIENT SHOULD KNOW IN CASE HE/SHE MISSES A DOSE

If you have to receive the medicine continuously and you miss a dose, you should receive it as soon as possible. However, if time for the next dose approaches, do not receive the dose you have missed but continue treatment as usual.

Do not double doses.

2.10 THINGS THE PATIENT SHOULD KNOW ABOUT PRODUCT EXPIRY DATE

The expiry date is inscribed on the outer and inner package. In case the inscribed date has passed, do not use the medicine.

2.11 SPECIAL PRECAUTIONS FOR STORAGE

Keep at temperature <25° C and out of the reach and sight of children.

2.12 DATE OF FINAL REVISION OF THE PACKAGE LEAFLET

Prot. No.: 59140/19-12-2003

3. INFORMATION REGARDING THE CORRECT USE OF MEDICINES

•This medicine has been prescribed to you by your doctor and only for your specific medical problem. You should not give it to other people or use it for a different disease, without consulting your doctor first. •In case during treatment, any problem appears regarding the medicine, notify your doctor or pharmacist. •If you have any questions regarding the information related to the medicine you receive or if you need to be better informed for your medical problem, do not hesitate to ask your doctor of pharmacist. •In order for the medicine administered to you to be effective and safe, it should be taken according to the given instructions. •For your safety and health, it is necessary to carefully read all information related to the medicine. •Do not keep medicines in bathroom cupboards because heat and moisture may alter them and place them as harmful for your health. •Do not keep medicines you no longer need or medicines that have expired. •Keep all medicines out of the reach and sight of children.

4. METHOD OF DISTRIBUTION

ATTENTION: Isotretinoin is TERATOGENIC. It should be received ONLY with a dermatologist's prescription (keep prescription for two years). In case you have obtained the medicine without a prescription and you have no instructions by a specialized dermatologist, before receiving any amount of the medicine, contact one of the following centers for more information:

1. Hospital "ANDREAS SYGROS", Athens, Tel. +30.210.7239611
2. Hospital of "INFECTIOUS DISEASES", Athens, Tel. +30.210.5613572
3. Hospital of "VENEREAL AND SKIN DISEASES", Thessalonica, Tel. +30.2310.811935, 2310.811191.

5. MARKETING AUTHORIZATION NUMBER:

A-Cnotren Caps. Soft 20mg: 64414/05/21.3.2006