Acnogen®

Isotretinoin

Isotretinoin 10mg & 20mg per capsule

1.1 Name of the medicinal product: Acnogen/Genepharm

1.2 Composition: Active Substance: Isotretinoin. Exipients: Hydrogenated soya oil, soya oil, partially hydrogenated soya oil, yellow bees wax. Composition of empty capsule: • **10mg/cap:** Gelatine, glycerine, titanium dioxide E171, CI 77891, partially hydrolysed maize starch, iron oxide (red) E172, CI 77491 • **20mg/cap:** Gelatine, glycerine, titanium dioxide E171, CI 77491, partially hydrolysed maize starch, ponceau 4R E124 CI 16255

1.3 Pharmaceutical form: Soft gelatin capsule

1.4 Content in active substance: Each capsule contains 10mg or 20mg Isotretinoin.

1.5 Description – Packaging: Box that contains 3 blisters with 10 caps. each.

1.6 Pharmacotherapeutic group: Anti-acne preparations for systemic use.

1.7 Marketing Authorization Holder: GENEPHARM S.A. - 18 km., Marathon Avenue, 153 51 Pallini, Attica-Greece

1.8 Manufacturer: ALCALA FARMA SL - Ctra. M-300, Km 29, 920, 28802 Alcala de Henares, MADRID-SPAIN

2. WHAT YOU SHOULD KNOW ABOUT THE DRUG PRESCRIBED TO YOU BY YOUR DOCTOR

2.1 Indications: Acnogen/Genepharm capsules are indicated for the treatment of severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring), resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.

2.2 Contraindications: Acnogen/Genepharm is contraindicated in women who are pregnant or breastfeeding.

Acnogen/Genepharm is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met.

Acnogen/Genepharm is also contraindicated in patients: • With hepatic insufficiency • With excessively elevated blood lipid values. • With hypervitaminosis A • With hypersensitivity to isotretinoin or to any of the excipients (the medicine contains hydrogenated soya oil). It is possible that some patients who are allergic to peanuts may suffer cross reactivity to products containing soya protein • Receiving concomitant treatment with tetracyclines.

2.3 Special warnings and precautions for use

2.3.1 General

Pregnancy Prevention Programme

This medicinal product is TERATOGENIC: Acnogen/Genepharm is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met: • She has severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy. • 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 duration of treatment and 1 month after the end of treatment. At least one and preferably two complementary forms of contraception including a barrier method should be used. • Even if she has amenorrhea she must follow all of the advice on effective contraception.

• She should be capable of complying with effective contraceptive measures. • She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy. • She understands the need and accepts to undergo pregnancy testing before, during and 5 weeks after the end of treatment. • She has acknowledged that she has understood the hazards and necessary precautions associated with the use of isotretinoin.

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.

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 has used at least one and preferably two methods of effective contraception including a barrier method 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 5 weeks after the end of treatment. The dates and results of pregnancy tests should be documented.

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.

As a minimum requirement, female patients at potential risk of pregnancy must use at least one effective method of contraception. Preferably the patient should use two complementary forms of contraception including a barrier method. Contraception should be continued for at least 1 month after stopping treatment with isotretinoin, even in patients with amenorrhea.

Pregnancy testing: According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25mIU/mL are recommended to be performed in the first 3 days of the menstrual cycle, as follows.

Prior to starting therapy: In order to exclude the possibility of pregnancy prior to starting contraception, it is recommended that an initial medically supervised pregnancy test should be performed and its date and result recorded. In patients without regular menses, the timing of this pregnancy test should reflect the sexual activity of the patient and should be undertaken approximately 3 weeks after the patient last had unprotected sexual intercourse. The prescriber should educate the patient about contraception. A medically supervised pregnancy test should also be performed during the consultation when isotretinoin is prescribed or in the 3 days prior to the visit to the prescriber, and should have been delayed until the patient had been using effective contraception for at least 1 month. This test should ensure the patient is not pregnant when she starts treatment with isotretinoin.

Follow-up visits: Follow-up visits should be arranged at 28 day intervals. The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient's sexual activity and recent menstrual history (abnormal menses, missed periods or amenorrhea). Where indicated, 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: Five weeks after stopping treatment, women should undergo a final pregnancy test to exclude pregnancy.

Prescribing and dispensing restrictions

Prescriptions of isotretinoin for women of childbearing potential should be limited to *30 days* of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of isotretinoin should occur on the same day. Dispensing of isotretinoin should be completed within a maximum of 7 days of the prescription.

Male patients: The available data suggests that the level of maternal exposure from the semen of the patients receiving isotretinoin is not of sufficient magnitude to be associated with the teratogenic effects of isotretinoin.

Male patients should be reminded that they must not share their medication with anyone, particularly not 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 isotretinoin because of the potential risk to the foetus of a pregnant transfusion recipient.

Psychiatric disorders: Depression, depression aggravated, aggressive tendencies, mood alterations, psychotic symptoms and, very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin. 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. However, discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

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 isotretinoin for a period of 5-6 months after the end of the treatment because of the risk of hypertrophic scarring in atypical areas and more rarely post inflammatory hyper or hypopigmentation in treated areas. Wax depilation should be avoided in patients on isotretinoin for at least a period of 6 months after treatment because of the risk of epidermal stripping.

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne 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 isotretinoin is likely to cause dryness of the skin and lips.

Eye disorders: Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. 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 also been reported and the onset in some patients was sudden. Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion. Withdrawal of isotretinoin may be necessary.

Musculo-skeletal and connective tissue disorders: Myalgia, arthralgia and increased serum creatine phosphokinase values have been reported in patients receiving isotretinoin, particularly in those undertaking vigorous physical activity.

Bone changes including premature epiphyseal closure, hyperostosis, and calcification of tendons and ligaments have occurred after several years of administration at very 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.

Benign intracranial hypertension: Cases of benign intracranial hypertension 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 papilloedema. Patients who develop benign intracranial hypertension should discontinue isotretinoin immediately.

Hepatobiliary disorders: Liver enzymes should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly 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, in the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.

Renal insufficiency: Renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Therefore, isotretinoin can be given to patients with renal insufficiency. However, it is recommended that patients are started on a low dose and titrated up to the maximum tolerated dose.

Lipid Metabolism: Serum lipids (fasting values) should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Elevated serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment and may also respond to dietary measures.

Isotretinoin has been associated with an increase in plasma triglyceride levels. Isotretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur. Levels in excess of 800mg/dL or 9mmol/L are sometimes associated with acute pancreatitis, which may be fatal.

Gastrointestinal disorders: Isotretinoin has been associated with inflammatory bowel disease (inlcuding regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing severe (haemorrhagic) diarrhoea should discontinue isotretinoin immediately. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Allergic reactions: Anaphylactic reactions have been rarely reported, in some cases 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 isotretinoin, 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 isotretinoin therapy.

2.3.2 Pregnancy and lactation

Pregnancy is an absolute contraindication to treatment with isotretinoin. 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.

Lactation: Isotretinoin is highly lipophilic, therefore the passage of isotretinoin into human milk is very likely. Due to the potential for adverse effects in the mother and exposed child, the use of isotretinoin is contraindicated in nursing mothers.

2.3.3 Effect on the ability to drive and use machines

A number of cases of decreased night vision have occurred during isotretinoin therapy and in rare instances have persisted after 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 machines.

2.3.4 Incompatibilities: None reported.

2.4 Drug interaction with other medicinal products and other forms of interaction

Patients should not take vitamin A as concurrent medication due to the risk of developing hypervitaminosis A.

Cases of benign intracranial hypertension (pseudotumor cerebri) have been reported with concomitant use of isotretinoin and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided.

2.5 Dosage and administration

Acnogen/Genepharm should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements. The capsules should be taken with food once or twice daily.

Adults including adolescents and the elderly: Acnogen/Genepharm therapy should be started at a dose of 0.5 mg/kg daily. The therapeutic response to isotretinoin and some of the adverse effects are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy. For most patients, the dose ranges from 0.5-1.0 mg/kg per day. Long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose. It has been shown that no substantial additional benefit is to be expected beyond a cumulative treatment dose of 120-150 mg/kg. The duration of treatment will depend on the individual daily dose. A treatment course of 16-24 weeks is normally sufficient to achieve remission.

In the majority of patients, complete clearing of the acne is obtained with a single treatment course. In the event of a definite relapse a further course of isotretinoin therapy may be considered using the same daily dose and cumulative treatment dose. As further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, a further course of treatment should not be considered until at least this period has elapsed.

Patients with severe renal insufficiency: In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 10 mg/day). The dose should then be increased up to 1 mg/kg/day or until the patient is receiving the maximum tolerated dose.

Children: Acnogen/Genepharm is not indicated for the treatment of prepubertal acne and is not recommended in patients less than 12 years of age.

Patients with intolerance: In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequences of a longer therapy duration and a higher risk of relapse. In order to achieve the maximum possible efficacy in these patients the dose should normally be continued at the highest tolerated dose.

2.6 Overdosage

Acnogen/Genepharm is a derivative of vitamin A. Although the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in cases of accidental overdose. Manifestations of acute vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with isotretinoin would probably be similar. These symptoms would be expected to be reversible and to subside without the need for treatment.

2.7 Undesirable effects

The following symptoms are the most commonly reported undesirable effects with isotretinoin: dryness of the mucosa e.g. of the lips, cheilitis, the nasal mucosa, epistaxis, and the eyes, conjunctivitis, dryness of the skin. Some of the side effects associated with the use of isotretinoin are dose-related. The side effects are generally reversible after altering the dose or discontinuation of treatment, however some may persist after treatment has stopped.

Infections:
Very Rare (≤1/10 000) Gram positive (mucocutaneous) bacterial infection

Blood and lymphatic system disorders:
Very common (≥1/10) Anaemia, Red blood cell sedimentation rate increased, Thrombocytopenia, Thrombocytosis
Common (≥1/100, <1/10) Neutropenia
Very Rare (≤1/10000) Lymphadenopathy

Immune system disorders:
Rare (≥1/10 000,<1/1000) Allergic skin reaction, Anaphylactic reactions, Hypersensitivity

Metabolism and nutrition disorders:
Very Rare (≤1/10000) Diabetes mellitus, Hyperuricaemia

Psychiatric disorders:
Rare (≥1/10 000,<1/1000) Depression, Depression aggravated, Aggressive tendencies, mood alterations
Very Rare (≤1/10000) Abnormal behaviour. Psychotic disorder. Suicidal ideation, Suicide attempt, Suicide

Nervous system disorders:
Common (≥1/100, <1/10) Headache
Very Rare (≤1/10 000) Benign intracranial hypertension. Convulsions, Drowsiness

Eye disorders:
Very common (≥1/10) Blepharitis, Conjunctivitis, Dry eye. Eye irritation
Very Rare (≤1/10000) Blurred vision, Cataract, Colour blindness (colour vision deficiencies). Contact lens intolerance Corneal opacity, Decreased night vision, Keratitis, Papilloedema (as sign of benign intracrania hypertension). Photophobia

Ear and labyrinth disorders:
Very Rare (≤1/10 000) Hearing impaired

Vascular disorders:
Very Rare (≤1/10000) Vasculitis (for example Wegener's granulomatosis, allergic vasculitis)

Respiratory, thoracic and mediastinal disorders:
Common (≥1/100, <1/10) Epistaxis, Nasal dryness, Nasopharyngitis
Very Rare (≤1/10000) Bronchospasm (particularly in patients with asthma), Hoarseness

Gastrointestinal disorders:
Very Rare (≤1/10000) Colitis, Ileitis, Dry throat, Gastrointestinal haemorrhage, haemorrhagic diarrhoea and inflammatory bowel disease, Nausea, Pancreatitis

Hepatobiliary disorders
Very common (≥1/10) Transaminase increased
Very Rare (≤1/10000) Hepatitis

Skin and subcutaneous tissues disorders:
Very common (≥1/10) Cheilitis, Dermatitis, Dry skin. Localised exfoliation, Pruritus,
Rare (≤1/10000,<l/1000) Rash erythematous, Skin fragility (risk of frictional trauma), Alopecia
Very Rare (≤1/10 000) Acne fulminans. Acne aggravated (acne flare). Erythema (facial). Exanthema, Hair disorders, Hirsutism, Nail dystrophy, Paronychia, Photosensitivity reaction, Pyogenic granuloma. Skin hyperpigmentation, Sweating increased

Musculo-skeletal and connective tissue disorders:
Very common (≥1/10) Arthralgia, Myalgia, Back pain (particularly adolescent patients)
Very Rare (≤1/10 000) Arthritis, Calcinosis (calcification of ligaments and tendons), Epiphyses premature fusion, Exostosis, (hyperostosis). Reduced bone density, Tendonitis

Renal and urinary disorders:
Very Rare (≤1/10 000) Glomerulonephritis

General disorders and administration site conditions:
Very Rare (≤1/10 000) Granulation tissue (increased formation of). Malaise

Investigations:
Very common (≥1/10) Blood triglycerides increased, High density lipoprotein, decreased
Common (≥1/100, <1/10) Blood cholesterol increased. Blood glucose increased, Haematuria, Proteinuria
Very Rare (≤1/10000) Blood creatine phosphokinase increased

The incidence of the adverse events was calculated from pooled clinical trial data involving 824 patients and from post-marketi data.

2.8 Missed dose: Not applicable.

2.9 Self life: It is printed on the inner and outer package. If the date has expired do not use the medicine.

2.10 Storage: Store at temperature below 25°C, in the original container, protected from light and humidity and keep out of the reach of children.

2.12 Instructions for use: Not applicable.

2.11 Date of last revision of the text: 03/03/2008

3. INFORMATION ON THE RATIONAL USE OF MEDICINES

• This drug was prescribed to you by your doctor only for your specific medical problem. You should not give it to other people use it for any other disease without first consulting your doctor. • If any problem with the medicine is experienced during the treatment, tell your doctor or your pharmacist immediately. • If you have any questions regarding the information concerning th medicine you are taking or if you need to be better informed about your medical problem, do not hesitate to request this information from your doctor or your pharmacist. • In order for the drug that has been prescribed to you to be effective and safe it must be taken according to the instructions given to you. • For your safety and good health, it is necessary to read carefully any information concerning the medicine that was administered to you. • Do not keep medicines in bathroom cabinets, becaus heat and humidity may spoil the medicine and render it harmful for your health. • Do not keep medicines that you do not need any more or that have already expired. • For increased safety, keep all medicines in a safe place away from children.

4. This medicine is given only under physician's prescription.

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