SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF MEDICINAL PRODUCT

Danol 200mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200mg of danazol

Also contains 76.6 mg of lactose monohydrate

For a full list of excipients see 6.1

3. PHARMACEUTICAL FORM

Capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Danol capsules are recommended for:

- Treatment of endometriosis amenable to hormonal management.
- Treatment of Hereditary angioedema.

4.2 Posology and Method of Administration

Adults:

Danol capsules should be given as a continuous course, dosage being adjusted according to the severity of the condition and the patient's response. A reduction in dosage once a satisfactory response has been achieved may prove possible. In fertile females, Danol capsules should be started during menstruation, preferably on the first day, to avoid exposing a pregnancy to its possible effects. Where doubt exists, appropriate checks should be made to exclude pregnancy before starting medication. Females of child-bearing age should employ non-hormonal contraception throughout the course of treatment.

In endometriosis the recommended dosage is 200mg to 800mg daily in a course of treatment lasting normally three to six months. Dosage should be increased if normal cyclical bleeding still persists after two months therapy, a higher dosage (not exceeding 800mg per day) may also be needed for severe disease.

For the prophylaxis of hereditary angioedema the recommended initial dose is 200mg two or three times a day until the desired initial response is obtained; then the maintenance dosage is determined by decreasing the initial dosage by 50% or less at intervals of one to three months or longer, depending on frequency of attacks prior to treatment.

Following a favourable response to Danol, the lowest effective maintenance dose should be sought for a continuous preventive treatment.

Daily dosage may be increased by up to 200mg if condition is not controlled at lower doses.

Elderly: Danol is not recommended.

Children: Danol is not recommended.

The capsules are for oral administration.

4.3 Contra-Indications

1. Pregnancy
2. Breast feeding
3. Markedly impaired hepatic, renal or cardiac function
4. Porphyria
5. Active thrombosis or thromboembolic disease and a history of such events
6. Androgen dependent tumour
7. Undiagnosed abnormal genital bleeding.
8. Hypersensitivity to danazol or to any of the excipients.
9. Concomitant administration with simvastatin (see section 4.5)

4.4 Special Warnings and Special Precautions for Use

Special Warnings

In the event of virilisation, Danol should be withdrawn. Androgenic reactions generally prove reversible, but continued use of Danol after evidence of androgenic virilisation increases the risk of irreversible androgenic effects.

Danol should be stopped if any clinically significant adverse event arises, and particularly if there is evidence of papilloedema, headache, visual disturbances or other signs or symptoms of raised intracranial pressure, jaundice or other indication of significant hepatic disturbance, thrombosis or thromboembolism.

Whilst a course of therapy may need to be repeated, care should be observed as no safety data are available in relation to repeated courses of treatment over time. The long-term risk of 17-alkylated steroids (including benign hepatic adenomata, hepatocellular focal nodular hyperplasia, peliosis hepatis and hepatic carcinoma), should be considered when danazol, which is chemically related to those compounds, is used.

Data, from two case-control epidemiological studies, were pooled to examine the relationship between endometriosis, endometriosis treatments and ovarian cancer. These preliminary results suggest that the use of danazol might increase the baseline risk of ovarian cancer in - patients treated for endometriosis.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Precautions

In view of its pharmacology, known interactions and side effects, particular care should be observed when using Danol in patients with hepatic or renal disease, hypertension or other cardiovascular disease and in any state which may be exacerbated by fluid retention as well as in diabetes mellitus, polycythaemia, epilepsy, lipoprotein disorder, and in those who have shown marked or persistent androgenic reaction to previous gonadal steroid therapy.

Caution is advised in patients with migraine.

Until more is known, caution is advised in the use of Danol in the presence of known or suspected malignant disease (see also contra-indications). Before treatment initiation, the presence of hormone–dependent carcinoma should be excluded at least by careful clinical examination, as well as if breast nodules persist or enlarge during danazol treatment.

In addition to clinical monitoring in all patients, appropriate laboratory monitoring should be considered which may include periodic measurement of hepatic function and haematological state. For long-term treatment (> 6 months) or repeated courses of treatment, biannual hepatic ultrasonography is recommended.

Danazol should be initiated during menstruation. An effective, non-hormonal method of contraception should be employed (see Section 4.2 and 4.6 Pregnancy and Lactation).

The lowest effective dose of Danol should always be sought.

4.5 Interactions with other medicinal products and other forms of Interaction

Anti-convulsant therapy: Danol may affect the plasma level of carbamazepine and possibly the patient's response to this agent and to phenytoin. With phenobarbital it is likely that similar interaction would occur.

Anti-diabetic therapy: Danol can cause insulin resistance.

Oral anti-coagulant therapy: Danol can potentiate the action of warfarin.

Anti-hypertensive therapy: Possibly through promotion of fluid retention, Danol can oppose the action of anti-hypertensive agents.

Ciclosporin and tacrolimus: Danol can increase the plasma level of ciclosporin and tacrolimus, leading to an increase of the renal toxicity of these drugs.

Concomitant steroids: Although specific instances have not been described, it is likely that interactions will occur between Danol and gonadal steroid therapy.

Migraine therapy: Danol may itself provoke migraine and possibly reduce the effectiveness of medication to prevent that condition.

Ethyl alcohol: Subjective intolerance in the form of nausea and shortness of breath has been reported.

Alpha calcidol: Danol may increase the calcaemic response in primary hypoparathyroidism necessitating a reduction in dosage of this agent.

Interactions with laboratory function tests: Danazol treatment may interfere with laboratory determination of testosterone or plasma proteins (See also section4.8 Undesirable effects)

Statins: The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with statins metabolised by CYP3A 4.The concomitant administration of Danazol with simvastatin is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

There is epidemiological and toxicological evidence of hazard in human pregnancy. Danazol is known to be associated with the risk of virilisation to the female foetus if administered during human pregnancy. Danazol should not be used during pregnancy. Women of childbearing age should be advised to use an effective, non-hormonal, method of contraception. If the patient conceives during therapy, danazol should be stopped. Danazol has the theoretical potential for androgenic effects in breast-fed infants and therefore either danazol therapy or breast-feeding should be discontinued.

4.7 Effects on Ability to Drive and Use Machines

Danol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable Effects

Blood and lymphatic system disorders

Increase in red cell and platelet count. Reversible polycythaemia, leucopoenia, thrombocytopenia, eosinophilia and splenic peliosis.

Endocrine disorders

Androgenic effects:

Acne, weight gain, increased appetite, seborrhoea, hirsutism, hair loss, voice change, which may take the form of hoarseness, sore throat or of instability or deepening of pitch. Hypertrophy of the clitoris, fluid retention.

Other endocrine effects:

Menstrual disturbances in the form of spotting, alteration of the timing of the cycle and amenorrhoea. Flushing, vaginal dryness, changes in libido, vaginal irritation and reduction in breast size.

Modest reduction in spermatogenesis.

Metabolism and nutrition disorders

Increased insulin resistance, increase in plasma glucagon, mild impairment of glucose tolerance.

Increase in LDL cholesterol, decrease in HDL cholesterol, affecting all subfractions, and decrease in apolipoproteins AI and AII.

Induction of aminolevulinic acid (ALA) synthetase, and reduction in thyroid binding globulin, T4, with increased uptake of T3 but without disturbance of thyroid stimulating hormone or free levothyroxine index.

Psychiatric disorders

Emotional lability, anxiety, depressed mood and nervousness.

Nervous system disorders

Dizziness, headache, vertigo, benign intracranial hypertension, migraine.

Aggravation of epilepsy, carpal tunnel syndrome.

Eye disorders

Visual disturbances such as blurring of vision, difficulty in focusing, difficulty in wearing contact lenses and refraction disorders requiring correction.

Respiratory, thoracic and mediastinal disorders

Pleuritic pain, interstitial pneumonitis.

Gastrointestinal disorders

Nausea, epigastric pain.

Cardiac disorders

Hypertension, palpitations and tachycardia.

Thrombotic events including sagittal sinus, cerebrovascular thrombosis as well as arterial thrombosis. Myocardial infarction.

Hepatobiliary disorders

Isolated increases in serum transaminase levels, cholestatic jaundice, benign hepatic adenomata and pancreatitis. Peliosis hepatitis as well as malignant hepatic tumour observed with long term use.

Hepatocellular injury, hepatic failure, jaundices hepatocellular, hepatocellular focal nodular hyperplasia.

Skin and subcutaneous tissue disorders

Rashes, which may be maculopapular, petechial or purpuric and may be accompanied by fever or may take an urticarial form and may be accompanied by facial oedema. Sun-sensitive rash.

Inflammatory erythematosus nodules, changes in skin pigmentation, exfoliative dermatitis and erythema multiforme.

Musculoskeletal and connective tissue disorders

Backache and muscle cramps which can be severe, with elevation of creatine phosphokinase levels. Muscle tremors, fasciculation, limb pain, joint pain and joint swelling.

Renal and urinary disorders

Haematuria with prolonged use in patients with hereditary angioedema.

General disorders and administration site conditions

Fatigue.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9. Overdose

Available evidence suggests that acute overdosage would be unlikely to give rise to immediate serious reaction.

In the case of acute overdose, consideration should be given to reducing the absorption of the drug with activated charcoal and the patient should be kept under observation in case of any delayed reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system, antigonadotropins and similar agents, ATC code: G03XA01.

Danazol, 17a-pregna-2,4-dien-20-yno(2,3-d)-isoxazol-17-ol, is a synthetic steroid derived from ethisterone. Its pharmacological properties include:

1. Relatively marked affinity for androgen receptors, less marked affinity for progesterone receptors and least affinity for oestrogen receptors. Danazol is a weak androgen but in addition antiandrogenic, progestogenic, antiprogestogenic, oestrogenic and antioestrogenic actions have been observed.
2. Interference with the synthesis of gonadal steroids, possibly by inhibition of the enzymes of steroidogenesis, including 3β hydroxysteroid dehydrogenase,17β hydroxysteroid dehydrogenase, 17 hydroxylase, 17, 20 lyase, 11β hydroxylase, 21 hydroxylase and cholesterol side chain cleavage enzymes, or alternatively by inhibition of the cyclic AMP accumulation usually induced by gonadotrophic hormones in granulosa and luteal cells.
3. Inhibition of the mid-cycle surge of FSH and LH as well as alterations in the pulsatility of LH. Danazol can also reduce the mean plasma levels of these gonadotrophins after the menopause.
4. A wide range of actions on plasma proteins, including increasing prothrombin, plasminogen, antithrombin III, alpha-2 macroglobulin, C1 esterase inhibitor, and erythropoietin and reducing fibrinogen, thyroid binding and sex hormone binding globulins. Danazol increases the proportion and concentration of testosterone carried unbound in plasma.
5. The suppressive effects of danazol on the hypothalmic-pituitary-gonadal axis are reversible, cyclical activity reappearing normally within 60-90 days after therapy.

5.2 Pharmacokinetic Properties

Danazol is absorbed from the gastrointestinal tract, peak plasma concentrations of 50-80ng/ml being reached approximately 2-3 hours after dosing. Compared to the fasting state, the bioavailability has been shown to increase 3 fold when the drug is taken with a meal with a high fat content. It is thought that food stimulates bile flow which facilitates the dissolution and absorption of danazol, a highly lipophilic compound.

The apparent plasma elimination half-life of danazol in a single dose is approximately 3-6 hours. With multiple doses this may increase to approximately 26 hours.

None of the metabolites of danazol, which have been isolated, exhibits pituitary inhibiting activity comparable to that of danazol.

Few data on excretion routes and rates exist. In the monkey 36% of a radioactive dose was recoverable in the urine and 48% in the faeces within 96 hours.

5.3 Preclinical Safety Data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Capsule

Maize starch

Lactose monohydrate

Talc

Magnesium stearate

Capule Shell

Gelatin

Titanium dioxide (E171)

Red iron oxide (E172)

Yellow iron oxide (E172)

Black Ink which contains:

Shellac glaze 45% (20% esterfied) in ethanol, black iron oxide (E172), propylene glycol, ammonium hydroxide 28%.

OR

Shellac, propylene glycol, strong ammonia solution, potassium hydroxide, black iron oxide (E 172).

6.2 Special Precautions for Storage

Store below 30^0C.

7. MANUFACTURER

Zentiva K.S., Prague, Czech Republic or Sanofi Synthelabo LTD., UK.

8. LICENSE HOLDER

Sanofi-aventis Israel ltd. POB 8090 Netanya 4250499.