DANOGEN Capsules (Danazol)

**Composition**

**DANOGEN 50**
Each capsule contains:
Danazol...50 mg

**DANOGEN 100**
Each capsule contains:
Danazol...100 mg

**DANOGEN 200**
Each capsule contains:
Danazol...200 mg

**Dosage Form**

Capsules for oral use.

**Pharmacology**

**Pharmacodynamics**

Danazol suppresses the pituitary-ovarian axis. This suppression is probably a combination of depressed hypothalamic-pituitary response to lowered oestrogen production, the alteration of sex-steroid metabolism, and interaction of danazol with sex hormone receptors. The only other demonstrable hormonal effect is weak androgenic activity. Danazol depresses the output of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

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

- Relatively marked affinity for androgen receptors, less marked affinity for progesterone receptors and least affinity for oestrogen receptors. In addition, anti-androgenic, progestogenic, anti-progestogenic, oestrogenic and anti-oestrogenic actions have been observed with danazol.
- 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.
- Inhibition of the midcycle surge of FSH and LH as well as alterations in the pulsatility of LH. Danazol can also reduce the mean plasma levels of these gonadotropins after menopause.
- A wide range of actions on plasma proteins, including increasing prothrombin, plasminogen, antithrombin III, alpha2-macroglobulin, C1 esterase inhibitor, and erythropoietin and reducing

Danazol...
fibrinogen, thyroid binding and sex hormone-binding globulins. Danazol increases the proportion and concentration of testosterone carried unbound in plasma.

The suppressive effects of danazol on the hypothalamic-pituitary-gonadal axis are reversible, cyclical activity reappearing normally within 60-90 days after therapy.

Recent evidence suggests a direct inhibitory effect at gonadal sites and a binding of danazol to receptors of gonadal steroids at target organs. In addition, danazol has been shown to significantly decrease IgG, IgM and IgA levels, as well as phospholipid and IgG isotope autoantibodies in patients with endometriosis and associated elevations of autoantibodies, suggesting this could be another mechanism by which it facilitates regression of the disease.

In the treatment of endometriosis, danazol alters the normal and ectopic endometrial tissue so that it becomes inactive and atrophic. Complete resolution of endometrial lesions occurs in the majority of cases. Changes in vaginal cytology and cervical mucus reflect the suppressive effect of danazol on the pituitary-ovarian axis.

In the treatment of fibrocystic breast disease, danazol usually produces partial to complete disappearance of nodularity and complete relief of pain and tenderness. Changes in the menstrual pattern may occur. Generally, the pituitary-suppressive action of danazol is reversible. Ovulation and cyclic bleeding usually return within 60-90 days when therapy with danazol is discontinued.

In the treatment of hereditary angio-oedema, danazol at effective doses prevents attacks of the disease characterized by episodic oedema of the abdominal viscera, extremities, face, and airway which may be disabling and, if the airway is involved, fatal. In addition, danazol corrects partially or completely the primary biochemical abnormality of hereditary angio-oedema by increasing the levels of the deficient C1 esterase inhibitor (C1EI). As a result of this action the serum levels of the C4 component of the complement system are also increased.

### Pharmacokinetics

#### Absorption

After oral administration of a 400 mg dose to healthy male volunteers, peak plasma concentrations of danazol are reached between 2 and 8 hours, with a median $T_{\text{max}}$ value of 4 hours. Steady-state conditions are observed following 6 days of twice daily dosing of danazol.

The pharmacokinetic parameters for danazol after administering a 400 mg oral dose to healthy males are summarized in the following table:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>69.6 ± 29.9</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>2.47 ± 1.62</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng*h/mL)</td>
<td>601 ± 181</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>9.70 ± 3.29</td>
</tr>
<tr>
<td>Total Body Clearance (L/h)</td>
<td>727 ± 221</td>
</tr>
</tbody>
</table>

The pharmacokinetic parameters for danazol after oral administration of 100, 200 and 400 mg single doses to healthy female volunteers are summarized in the following table:

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Mean $C_{\text{max}}$ ± SD (ng/mL)</th>
<th>Mean $T_{\text{max}}$ (h)</th>
<th>Mean $AUC_{0-\infty}$ ± SD (ng*h/mL)</th>
</tr>
</thead>
</table>
Dose Proportionality

Bioavailability studies indicate that blood levels do not increase proportionally with increases in the administered dose. Single-dose administration of danazol in healthy female volunteers found that a 4-fold increase in dose produced only a 1.6- and 2.5-fold increase in AUC and a 1.3 and 2.2-fold increase in C<sub>max</sub> in the fasted and fed states, respectively. A similar degree of non-dose-proportionality was observed at steady state.

Food Effect

Single dose administration of 100 mg and 200 mg capsules of danazol to female volunteers showed that both the extent of availability and the maximum plasma concentration increased by 3-to 4-fold, respectively, following a meal (>30 grams of fat), when compared to the fasted state. Further, food also delayed mean time to peak concentration of danazol by about 30 minutes. It is thought that food stimulates bile flow, which facilitates the dissolution and absorption of danazol, a highly lipophilic compound.

Even after multiple dosing under less extreme food/fasting conditions, there remained approximately a 2-to 2.5-fold difference in bioavailability between the fed and fasted states.

Distribution

Danazol is lipophilic and can partition into cell membranes, indicating the likelihood of distribution into deep tissue compartments.

Metabolism and Excretion

Danazol appears to be metabolized and the metabolites are eliminated by renal and faecal pathways. The two primary metabolites excreted in the urine are 2-hydroxymethyl danazol and ethisterone. At least ten different products were identified in faeces. The reported elimination half-life of danazol is variable across studies. The mean half-life of danazol in healthy males is 9.7 hours. After 6 months of 200 mg three times--day dosing in endometriosis patients, the half-life of danazol was reported as 23.7 hours.

Indications

Endometriosis: Treatment of endometriosis where the required end-point of treatment is fertility, or for the control of symptoms when surgery is contraindicated or has been unsuccessful. To control pain, pelvic tenderness and other associated symptoms and to resolve or reduce the extent of endometriotic foci. Treatment of endometriosis is associated symptoms or/and to reduce the extent of endometriosis foci. Danazol may be used either in conjunction with surgery or, as sole hormonal therapy, in patients not responding to other treatments.

Severe Cyclical Mastalgia: With or without nodularity (fibrocystic disease), unresponsive to counselling or analgesics, to reduce pain, tenderness and nodularity.

Breast Cysts: Control of benign, multiple or recurrent breast cysts in conjunction with aspiration.

Dysfunctional Uterine Bleeding (DUB): In DUB presenting as menorrhagia, to control excessive blood loss, to control associated dysmenorrhoea.

Symptomatic Gynaecomastia: Both idiopathic and drug induced, to reduce the size of breast, to control pain and tenderness.
DANOGEN should be given as a continuous course, with 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, DANOGEN 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 childbearing age should employ non-hormonal contraception throughout the course of treatment.

Endometriosis: In patients infertile due to endometriosis, a starting dose of 800 mg given in two divided doses is recommended. Amenorrhoea and rapid response to painful symptoms is best achieved at this dosage level. Gradual downward titration to a dose sufficient to maintain amenorrhoea may be considered depending upon patient response. For mild cases, an initial daily dose of 200-400 mg given in two divided doses is recommended and may be adjusted depending on patient response. 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. Therapy should begin during menstruation. Otherwise, appropriate tests should be performed to ensure that the patient is not pregnant while on therapy with danazol. It is essential that therapy continue uninterrupted for 3-6 months but may be extended to 9 months if necessary. After termination of therapy, if symptoms recur, treatment can be reinstated.

Severe Cyclical Mastalgia: 200-300 mg daily; for 3-6 months.

Fibrocystic Breast Disease: The total daily dosage of danazol for fibrocystic breast disease ranges from 100-400 mg given in two divided doses depending upon patient response. Therapy should begin during menstruation. Otherwise, appropriate tests should be performed to ensure that the patient is not pregnant while on therapy with danazol. A non-hormonal method of contraception is recommended when danazol is administered at this dose, since ovulation may not be suppressed. In most instances, breast pain and tenderness are significantly relieved by the first month and eliminated in 2-3 months. Usually, elimination of nodularity requires 4-6 months of uninterrupted therapy. Regular menstrual patterns, irregular menstrual patterns, and amenorrhoea each occur in approximately one-third of patients treated with 100 mg of danazol. Irregular menstrual patterns and amenorrhoea are observed more frequently with higher doses. Clinical studies have demonstrated that 50% of patients may show evidence of recurrence of symptoms within 1 year. In this event, treatment may be reinstated.

Benign Breast Cysts: 300 mg daily for 3-6 months.

DUB: 200 mg daily for 3 months.

Gynaecomastia: 200 mg daily in adolescents, which may be increased to 400 mg daily if no response is obtained after 2 months. Adults may be given 400 mg daily for 6 months.

Preoperative Thinning of the Endometrium: The usual dose is 400-800 mg daily given as a continuous course for 3-6 weeks.

Hereditary Angioneurotic Oedema: The dosage requirements for continuous treatment of hereditary angio-oedema with danazol should be individualized on the basis of the clinical response of the patient. It is recommended that the patient be started on 200 mg, two or three times a day. After a favourable initial response is obtained in terms of prevention of episodes of oedematous attacks, the proper continuing dosage should be determined by decreasing the dosage by 50% or less at intervals of 1-3 months or longer if
frequency of attacks prior to treatment dictates. If an attack occurs, the daily dosage may be increased by up to 200 mg. During the dose adjusting phase, close monitoring of the patient's response is indicated, particularly if the patient has a history of airway involvement.

### Contraindications

Danazol should not be administered to patients with the following:

- Undiagnosed abnormal genital bleeding
- Markedly impaired hepatic, renal, or cardiac function
- Pregnancy
- Breastfeeding
- Porphyria – danazol can induce ALA synthetase activity and, hence, porphyrin metabolism
- Androgen-dependent tumour
- Active thrombosis or thromboembolic disease and history of such events
- Hypersensitivity to danazol or to any of the excipients

### Warnings And Precautions

#### General

Use of danazol in pregnancy is contraindicated. A sensitive test (e.g. beta subunit test if available) capable of determining early pregnancy is recommended immediately prior to start of therapy. Additionally a non-hormonal method of contraception should be used during therapy. If a patient becomes pregnant while taking danazol, administration of the drug should be discontinued and the patient should be apprised of the potential risk to the foetus. Exposure to danazol *in utero* may result in androgenic effects on the female foetus; reports of clitoral hypertrophy, labial fusion, urogenital sinus defect, vaginal atresia, and ambiguous genitalia have been received.

Thromboembolism, thrombotic and thrombophlebitic events, including sagittal sinus thrombosis and life-threatening or fatal strokes, have been reported.

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, peliosishepatis and hepatic carcinoma), have been observed with long-term use and should be considered when danazol, which is chemically related to those compounds, is used. Peliosishepatis and hepatic adenoma may be silent until complicated by acute, potentially life-threatening intraabdominal haemorrhage. The physician, therefore, should be alert to this possibility.

Attempts should be made to determine the lowest dose that will provide adequate protection. If the drug was begun at a time of exacerbation of hereditary angioneurotic oedema due to trauma, stress or other cause, periodic attempts to decrease or withdraw therapy should be considered.

Danazol has been associated with several cases of benign intracranial hypertension also known as pseudotumourcerebri. Early signs and symptoms of benign intracranial hypertension include papilloedema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilloedema and, if present, they should be advised to discontinue danazol immediately and be referred to a Neurologist for further diagnosis and care. Danazol should also be stopped if other signs or symptoms of raised intracranial pressure, jaundice or other indication of significant hepatic disturbance, thrombosis or thromboembolism occur.

In the event of virilization, danazol should be withdrawn. Androgenic reactions generally prove reversible,
but continued use of danazol after evidence of androgenic virilization increases the risk of irreversible androgenic effects, even when the drug administration is stopped. A temporary alteration of lipoproteins in the form of decreased high-density lipoproteins and, possibly, increased low-density lipoproteins has been reported during danazol therapy. These alterations may be marked, and prescriber should consider the potential impact on the risk of atherosclerosis and coronary artery disease in accordance with the potential benefit of the therapy to the patient. Until more is known, caution is advised in the use of danazol in the presence of known or suspected malignant disease. Before initiating therapy of fibrocystic breast disease with danazol, carcinoma of the breast should be excluded. However, nodularity, pain and tenderness due to fibrocystic breast disease may prevent recognition of underlying carcinoma before treatment is begun. Therefore, if any nodule persists or enlarges during treatment, hormone-dependent carcinoma should be considered and ruled out at least by careful clinical examination before initiating therapy with danazol. In view of its pharmacology, known interactions and side effects, particular care should be observed when using danazol in patients with hepatic or renal disease, hypertension or other cardiovascular disease and in any state that 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. Since hepatic dysfunction manifested by modest increases in serum transaminases levels has been reported in patients treated with danazol, periodic liver function tests should be performed. 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. Administration of danazol has been reported to cause exacerbation of the manifestations of acute intermittent porphyria. 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. Patients should be watched closely for signs of androgenic effects, some of which may not be reversible even when drug administration is stopped. Because danazol may cause some degree of fluid retention, conditions that might be influenced by this factor, such as epilepsy, migraine, or cardiac or renal dysfunction, polycythaemia and hypertension require careful observation. Use with caution in patients with diabetes mellitus. Laboratory monitoring of the haematologic state should be considered. Lactose Intolerance Each tablet of this medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine. Drug Interactions Prolongation of prothrombin time occurs in patients stabilized on warfarin. Therapy with danazol may cause an increase in carbamazepine levels in patients taking both drugs. Danazol 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 a similar interaction would occur. Danazol can cause insulin resistance. Caution should be exercised when used with antidiabetic drugs. Danazol may raise the plasma level of cyclosporin and tacrolimus, leading to an increase of the renal
toxicity of these drugs. Monitoring of systemic concentrations of these drugs and appropriate dose adjustments may be needed when used concomitantly with danazol. Danazol can increase the calcaemic response to alpha-calcidol in primary hypoparathyroidism. The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with statins metabolized by CYP3A4 such as simvastatin, atorvastatin and lovastatin. Caution should be exercised if used concomitantly. Consult the product labelling for statin drugs for specific information on dose restrictions in presence of danazol. Possibly through promotion of fluid retention, danazol can oppose the action of anti-hypertensive agents. Although specific instances have not been described, it is likely that interactions will occur between danazol and gonadal steroid therapy. Danazol may itself provoke migraine and possibly reduce the effectiveness of medication to prevent that condition. Subjective intolerance in the form of nausea and shortness of breath has been reported.

Laboratory Tests

Danazol treatment may interfere with laboratory determinations of testosterone, androstenedione, dehydroepiandrosterone, and plasma proteins. Other metabolic events include a reduction in thyroid-binding globulin and T4 with increased uptake of T3, but without disturbance of thyroid-stimulating hormone or of free-thyroxin index.

Pregnancy

Pregnancy Category X. There is epidemiological and toxicological evidence of hazard in human pregnancy. Danazol is known to be associated with the risk of virilization 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.

Lactation

Danazol has the theoretical potential for androgenic effects in breastfed infants and therefore either danazol therapy or breast-feeding should be discontinued.

Paediatric Use

Safety and effectiveness in paediatric patients have not been established.

Geriatric Use

Clinical studies of danazol did not include sufficient numbers of subjects aged 65 years and over to determine the safety and effectiveness of danazol in elderly patients.

Undesirable Effects

The following events have been reported in association with the use of danazol: Androgen-like effects include weight gain, acne and seborrhea. Mild hirsutism, oedema, hair loss, voice change, which may take the form of hoarseness, sore throat or of instability or deepening of pitch, may
occur and may persist after cessation of therapy. Hypertrophy of the clitoris is rare.

Other possible endocrine effects are menstrual disturbances including spotting, alteration of the timing of the cycle and amenorrhoea. Although cyclical bleeding and ovulation usually return within 60-90 days after discontinuation of therapy with danazol, persistent amenorrhoea has occasionally been reported. Flushing, sweating, vaginal dryness and irritation and reduction in breast size, may reflect lowering of oestrogen. Nervousness and emotional lability have been reported. In males, a modest reduction in spermatogenesis may be evident during treatment. Abnormalities in semen volume, viscosity, sperm count, and motility may occur in patients receiving long-term therapy.

Hepatic dysfunction, as evidenced by reversible elevated serum enzymes and/or jaundice, has been reported in patients receiving a daily dosage of danazol of 400 mg or more. It is recommended that patients receiving danazol be monitored for hepatic dysfunction by laboratory tests and clinical observation. Serious hepatic toxicity including cholestatic jaundice, peliosis hepatis, and hepatic adenoma has been reported. Abnormalities in laboratory tests may occur during therapy with danazol, including creatine phosphokinase (CPK), glucose tolerance, glucagon, thyroid-binding globulin, sex-hormone-binding globulin, other plasma proteins, lipids and lipoproteins.

The following reactions have been reported, but a causal relationship to the administration of danazol has neither been confirmed nor refuted:

Allergic: Urticaria, pruritus and, rarely, nasal congestion.

CNS Effects: Headache, nervousness and emotional lability, dizziness and fainting, depression, fatigue, sleep disorders, tremor, paraesthesias, weakness, visual disturbances, and rarely, benign intracranial hypertension, anxiety, changes in appetite, chills, and rarely convulsions, Guillain-Barré syndrome, aggravation of epilepsy.

Gastrointestinal: Gastroenteritis, nausea, vomiting, constipation and, rarely, pancreatitis and splenic peliosis, epigastric pain.

Musculoskeletal and Connective Tissue Disorders: Muscle cramps or spasms, or pains, joint pain, joint lockup, joint swelling, pain in back, neck, or extremities, with elevation of CPK levels, muscle tremors, fasciculation. Rarely, carpal tunnel syndrome, which may be secondary to fluid retention.

Cardiac Disorders: Hypertension, palpitations and tachycardia. Thrombotic events including sagittal sinus, cerebrovascular thrombosis as well as arterial thrombosis. Myocardial infarction.


Haematologic: An increase in red cell and platelet count. Reversible erythrocytosis, leucocytosis or polycythemia may be provoked. Eosinophilia, leucopenia, splenic peliosis and thrombocytopenia have also been noted.

Skin: Rashes (maculopapular, vesicular, papular, purpuric, petechial and may be accompanied by fever or may take an urticarial form and may be accompanied by facial oedema) and rarely, sun sensitivity, Stevens-Johnson syndrome, inflammatory erythematous nodules, changes in skin pigmentation, exfoliative dermatitis and erythema multiforme.

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

Respiratory, Thoracic and Mediastinal Disorders: Pleuritic pain, interstitial pneumonitis.

Hepatobiliary Disorders: Isolated increases in serum transaminase levels, cholestatic jaundice, benign hepatic adenomata and pancreatitis. Peliosis hepatitis as well as malignant hepatic tumour observed in rare instances with long-term use. Hepatocellular injury, hepatic failure, jaundice hepatocellular.

Metabolism and nutrition disorders: 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. Other: Increased insulin requirements in diabetic patients, change in libido, bleeding gums, fever, pelvic pain, and nipple discharge. Malignant liver tumours have been reported in rare instances after long term use.

**Overdosage**

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.

**Storage And Handling Instructions**

Protect from light.

**Packaging Information**

DANOGEN50 .................... Strip pack of 10 capsules
DANOGEN100 ................... Strip pack of 10 capsules
DANOGEN200 ................... Strip pack of 10 capsules

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DANOGEN Capsules

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