

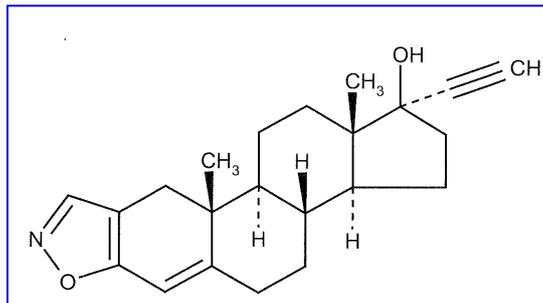
## PRODUCT INFORMATION

### NAME OF THE MEDICINE

Active ingredient: Danazol

Chemical name: 17 $\alpha$ -pregna-2,4-dien-20-yno(2,3-d)isoxazol-17 $\beta$ -ol

Structural formula:



Molecular formula: C<sub>22</sub>H<sub>27</sub>NO<sub>2</sub>

Molecular weight: 337.5

CAS Registry No.: 17230-88-5

### Description

Danazol is a synthetic hormone derived from ethisterone.

Danazol is a white or pale yellow crystalline powder. It is practically insoluble in water, but soluble in chloroform and in acetone. It has a melting point of 225°C with some decomposition.

Each Azol 100 capsule contains 100 mg of danazol. Azol 100 capsules also contain the following inactive ingredients: lactose, cellulose – microcrystalline, silica - colloidal anhydrous, povidone, lactose anhydrous, sodium starch glycolate, sodium lauryl sulfate, magnesium stearate, titanium dioxide, gelatin, iron oxide black.

Each Azol 200 capsule contains 200 mg of danazol. Azol 200 capsules also contains the following inactive ingredients: lactose anhydrous, erythrosine, lactose, sodium lauryl sulfate, iron oxide red, silica - colloidal anhydrous, sodium starch glycolate, cellulose – microcrystalline, titanium dioxide, povidone, magnesium stearate, gelatin, iron oxide yellow.

### Pharmacology

*Endometriosis and Menorrhagia.* In women of reproductive age, 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 the interaction of danazol with sex hormone receptors.

The only other demonstrable hormonal effect is weak androgenic activity and associated anabolic activity. No significant oestrogenic or progestational activity attributable to danazol has been found.

Danazol depresses the output of both follicle-stimulating hormone (FSH) and luteinising hormone (LH).

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.

The mechanism of action of danazol in the suppression of menstrual blood loss is not clear. However, danazol inhibits ovulation and plasma levels of oestradiol-17 $\beta$  fall. Whether endometrial proliferation is inhibited by reduced oestradiol levels or by a direct effect of danazol on endometrial oestrogen receptors is not known.

Generally, the pituitary suppressive action of danazol is reversible. When danazol treatment is discontinued, ovulation usually resumes within a few weeks as demonstrated by the major surge of LH and minor FSH surge that accompany ovulation.

*Hereditary Angioedema.* Hereditary angioedema (HAE) is associated with low serum levels of C<sub>1</sub> esterase inhibitor activity. Danazol administration results in increased levels of C<sub>1</sub> esterase inhibitor activity in serum, normal levels frequently being reached within one to two weeks of therapy. As a result of this, serum levels of C<sub>4</sub> also increase during danazol administration, frequently rising to the normal range.

Levels of albumin, C<sub>3</sub> and  $\alpha_2$ -macroglobulin show no statistically significant changes with danazol therapy; no increase in total serum protein occurs. The mechanism by which danazol increases the levels of C<sub>1</sub> esterase inhibitor activity and C<sub>4</sub> is unknown at present.

*Fibrocystic Breast Disease.* Danazol suppresses the ovulatory luteinising surge, interferes with gonadal steroidogenesis (directly and indirectly) and dampens the gonadotrophin response to luteinising hormone.

## Pharmacokinetics

Following oral administration and absorption, danazol is rapidly and extensively metabolised. However, plasma levels of unchanged danazol rise quickly, indicating a rapid onset of absorption. Peak plasma levels, varying between 2 and 8 hours, have been recorded in a number of studies. A considerable difference in peak plasma levels has been observed in individuals receiving the same dosage, and in bioavailability studies, levels do not increase in proportion to the administered dose. When the dose of danazol is doubled, the increase in plasma levels is about 35 to 40%.

Half-life of danazol has been estimated by different workers as 4.5, 6, 14.7 and 29 hours; however, wide differences occur among individual subjects.

Tissue distribution studies have demonstrated the continued presence of radioactivity in the intestines and stomach suggesting that danazol and its metabolites undergo enterohepatic circulation. No consistent localisation of this radioactivity has been found in any tissue other than the adrenal gland and the organs of excretion.

In humans, the major urinary metabolites of danazol are ethisterone and 2-hydroxymethylethisterone. Other minor urinary metabolites identified are  $\Delta$ -2-hydroxymethylethisterone, 6 $\beta$ -hydroxy-2-hydroxymethylethisterone and  $\Delta^1$ -6 $\beta$ -hydroxy-2-hydroxymethylethisterone. None of these metabolites have been found to exhibit antigonadotrophic activity.

Danazol has no significant effect on prolactin levels, or on thyroid, or adrenal function. Reduced serum thyroxine levels may occur and are attributed to competition between thyroxine and danazol for binding sites on thyroxine binding plasma proteins.

## Clinical Experience

*Endometriosis and Menorrhagia.* Clinically, the action of danazol has been demonstrated by human pharmacological studies and clinical trials. At a sufficiently high daily dose, danazol therapy results in inhibition of ovulation, suppression of menses, regressive changes of the vaginal mucosa and marked atrophy of the endometrium.

Vaginal spotting or bleeding may occur in some patients during therapy with danazol; in cases where it has been examined, this bleeding was associated with an atrophic endometrium.

Danazol therapy has been successful in the treatment of endometriosis, relief of the common presenting symptoms of dysmenorrhoea, pelvic pain and dyspareunia, resolution of ectopic endometrial implants and induration of the cul-de-sac has been obtained. Significant reversal of infertility associated with endometriosis has followed a course of danazol therapy.

Clinical studies have demonstrated the efficacy of danazol in the short-term management of menorrhagia. The reduction in blood loss continued for up to 3 months after stopping treatment. Other benefits have been relief of dysmenorrhoea, failure to influence menstrual cycle length, reduction in the number of days bleeding and a steady improvement in haemoglobin values despite the absence of iron therapy.

*Hereditary Angioedema.* In limited clinical trials, administration of danazol proved effective in the prevention of HAE attacks in patients of both sexes. In one double blind study with 9 patients, HAE attacks occurred in 44 of 47 placebo courses, but only one attack occurred during 46 danazol courses. Danazol effectively prevents attacks in HAE and acts to correct the associated biochemical abnormality.

*Fibrocystic Breast Disease.* Both placebo controlled and open studies with danazol in treating severe fibrocystic breast disease or mastalgia associated with severe breast disease have shown danazol to produce partial to complete disappearance of nodularity and complete relief of pain and tenderness. Limited studies suggest danazol to be effective in reducing breast cyst formation. Changes in the menstrual pattern may occur.

## Indications

*Endometriosis.* Treatment of visually proven (e.g. laparoscopy) endometriosis, where the required endpoint of treatment is fertility, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

*Menorrhagia.* Short-term (up to 6 months) management of intractable primary menorrhagia.

*Hereditary Angioedema.* Prophylaxis of attacks of hereditary angioedema of a severe or life-threatening nature, in male and female patients.

*Fibrocystic Breast Disease.* Short-term treatment (up to 6 months) of severe benign (fibrocystic) breast disease or mastalgia associated with severe symptomatic benign breast disease, in patients refractory to other treatments.

## Contraindications

- Undiagnosed abnormal genital bleeding
- Markedly impaired liver, renal or cardiac function, including oedema
- Past jaundice with oral contraceptives
- Undiagnosed ovarian/uterine masses
- Pelvic infection
- Neoplasia of primary or secondary sexual organs
- Hypertension WHO II or worse
- Known hypersensitivity to danazol
- Pregnancy\*
- Breastfeeding\*
- Porphyria (danazol can induce ALA synthetase activity and hence porphyrin metabolism)
- Androgen-dependent tumour
- Active thrombosis, thromboembolic disease or history of such events.

[\* see **Use in Pregnancy and Use in Lactation**].

## PRECAUTIONS

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

Experience with long-term danazol therapy is limited. Serious toxicity (including cholestatic jaundice) has been reported. Peliosis hepatitis, benign hepatic adenoma and hepatic carcinoma have been observed with long-term use. Peliosis hepatitis, hepatic adenoma and hepatic carcinoma may be silent until complicated by acute, potentially life-threatening intra-abdominal haemorrhage. The physician therefore should be alert to this possibility. In patients with HAE, 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 HAE 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 pseudotumour cerebri. 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, should be advised to discontinue danazol immediately and be referred to a neurologist for further diagnosis and care.

Patients should be watched closely for signs of androgenic effects and warned to report voice change promptly, as this effect may persist even when drug administration has stopped. Specific caution should be exercised when considering the use of danazol in professional singers.

Danazol should be stopped if there is evidence of virilisation (failure to stop danazol increases the risk of irreversible androgenic effects).

A treatment related 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 hence the potential impact on the risk of atherosclerosis and coronary artery disease in accordance with the potential benefit of the therapy to the patient should be considered. Clinical evidence suggests that on cessation of danazol therapy, plasma lipoprotein levels return to pre-treatment levels.

Patients taking danazol may show decreased glucose tolerance. The significance of this aberration for diabetic patients taking danazol is not known, but such patients should be carefully monitored.

Before initiating treatment, a thorough medical history and examination of abdomen, breast and pelvis should be undertaken to exclude the presence of carcinoma. During treatment, if breast nodules persist or enlarge, the presence of carcinoma should be excluded before continuing danazol.

Preliminary epidemiological data suggest that the use of danazol in patients undergoing treatment for endometriosis may increase the baseline risk of ovarian cancer.

Fluid retention may be produced to such a degree as to necessitate the use of diuretics. However, in some cases, fluid retention may be controlled by restriction of salt intake. Patients with conditions which may be influenced by fluid retention, such as epilepsy, migraine or cardiac or renal dysfunction, require careful observation.

Since hepatic dysfunction manifested by modest increases in serum transaminase levels and/or jaundice has been reported in patients treated with danazol, periodic liver function tests and close monitoring should be performed (see **Precautions** and **Adverse Effects**).

Periodic blood counts should be performed.

Administration of danazol has been reported to cause exacerbation of the manifestations of acute intermittent porphyria (see **Contraindications**).

While a course of therapy may need to be repeated, care should be observed. The risk of long-term exposure to 17-alkylated steroids should be borne in mind since danazol is chemically related to these compounds.

Danazol should be stopped if any clinically significant adverse event arises, and particularly if there is any evidence of jaundice or other indication of significant hepatic disturbance, thrombosis or thromboembolism. The lowest effective dose of danazol should be sought.

In view of its pharmacology, known interactions and side effects, particular care should be observed in using danazol in those with hepatic disease, hypertension or other cardiovascular disease, lipoprotein disorder, polycythemia, a history of marked or persistent androgenic reaction to previous gonadal steroid therapy, or epilepsy induced or worsened by previous gonadal steroid therapy. However, close clinical monitoring is advised in all patients.

See also **Instructions to Patients**.

### **Use in Pregnancy (Category D)**

Danazol inhibits ovulation in many women but pregnancies can occur if barrier contraception is not used. Virilisation of the foetus can result from use beyond the 8th week of pregnancy. Therefore it is essential that barrier methods of contraception are used during danazol treatment.

Pregnancy should be excluded before commencing therapy and treatment should be commenced during menstruation. A non-hormonal method of contraception should be recommended.

If a patient becomes pregnant during treatment, administration of danazol should be discontinued and the patient should be apprised of the potential risk to the foetus. If a patient suspects she has become pregnant during treatment, she should cease taking danazol and consult her physician. Exposure to danazol *in utero* may result in androgenic effects on the female foetus; reports to date comprise clitoral hypertrophy, labial fusion, urogenital sinus defect, vaginal atresia and ambiguous genitalia.

*Australian categorisation definition of Category D.* Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

### **Use in Lactation**

It is not known if danazol is excreted in breast milk or whether it has a harmful effect on the newborn. Therefore, it is not recommended for use in breastfeeding mothers.

### **Paediatric Use**

Safety and efficacy in children has not been established.

### **Interactions with Other Medicines**

*Warfarin.* Prolongation of prothrombin time occurs in patients stabilised on warfarin.

*Anticonvulsants.* Therapy with danazol may reduce the plasma clearance of carbamazepine, increasing its elimination half-life and plasma concentration and, may affect responsiveness to this agent and to phenytoin.

*Cyclosporin and Tacrolimus.* Danazol can increase the plasma levels of cyclosporin and tacrolimus.

*Oral Contraceptives.* Although no specific interaction has been recorded, it is recommended that oral contraceptives should not be used concurrently with danazol.

*Antidiabetic Therapy.* Danazol can cause insulin resistance.

*Concomitant Steroids.* It is likely that interactions between danazol and gonadal steroid therapy would occur.

*Antihypertensives.* Danazol can diminish the effectiveness of antihypertensive agents.

#### Effects on Laboratory Tests

Danazol treatment may interfere with laboratory determinations of testosterone, androstenedione, dehydroepiandrosterone or plasma proteins.

## Adverse Effects

In general, the side effects associated with danazol therapy are attributable to the pharmacological activity of the drug; these effects may reflect danazol's weak androgenic and anabolic activity and/or the gonadal suppression which results from therapy.

CIOMS frequency estimates: Very Common  $\geq 10\%$ , Common  $\geq 1$  to  $<10\%$ , Uncommon  $\geq 0.1$  to  $<1\%$ , Rare  $\geq 0.01$  to  $<0.1\%$ , Very rare  $<0.01\%$

### Androgenic/Anabolic Effects

*Very Common.* Acne (13%).

*Common.* Weight gain (4%), seborrhoea (2%), hirsutism (5%), oedema (6%) and hair loss. Voice change (3%), which may take the form of hoarseness, sore throat or of instability or deepening of the pitch (see **Precautions**).

*Rare.* Hypertrophy of the clitoris, fluid retention.

### Endocrine Effects

*Common.* Menstrual disturbances in the form of spotting, alteration of the timing of the cycle and amenorrhoea. Although cyclical bleeding and ovulation usually return within 60 to 90 days after discontinuation of danazol, persistent amenorrhoea has occasionally been reported.

Flushing (6%), sweating (3%), vaginal dryness and irritation (4%), may reflect lowering of oestrogen.

*Uncommon.* Changes in breast size.

*Very Rare.* Abnormalities in semen volume, viscosity, sperm count, and motility may occur in males receiving long-term therapy. Testicular atrophy may occur rarely.

### Hepatic Effects

*Uncommon.* Hepatic dysfunction, as evidenced by elevated serum enzymes and/or jaundice, has been reported in patients receiving a daily dosage of danazol of 400 mg or more.

*Rare.* Cholestatic jaundice, hepatic adenoma.

*Very Rare.* Peliosis hepatitis, malignant hepatic tumour.

### Biochemical Abnormalities

Alterations in values for laboratory tests may occur during danazol therapy, including: CPK, glucose tolerance, glucagon, sex hormone binding globulin, other plasma proteins, raised AST (SGOT), decreased PBI, blunted cyclical surges of LH, induction of amino levulinic acid (ALA) synthetase.

Other events include reduction in thyroid binding globulin and  $T_4$ , with increased uptake of  $T_3$  but without disturbance of thyroid stimulating hormone or of free thyroxine index.

Total cholesterol and LDL cholesterol may increase and high density lipoprotein cholesterol may decrease. A decrease in apolipoproteins AI and AII has been reported (see **Precautions**).

The following reactions have also been reported.

**Allergic**

Uncommonly. Urticaria and pruritus, and rarely nasal congestion.

**Dermatological**

*Common.* Rashes (3%) (maculopapular, vesicular, papular, purpuric, petechial), sometimes associated with facial oedema, fever or sun sensitivity.

*Very Rare.* Skin pigmentation, Stevens-Johnson syndrome, inflammatory erythematous nodules and erythema multiforme.

**Gastrointestinal**

*Common.* Nausea (2%), vomiting, constipation, indigestion, gastroenteritis.

*Rare.* Pancreatitis.

**Genitourinary**

*Very Rare.* Haematuria.

**Musculoskeletal**

*Common.* Muscle cramps, muscle tremors, spasms or pains, fasciculation, arthralgia, joint lock-up, joint swelling, and pain in back, neck or extremities.

*Very Rare.* Carpal tunnel syndrome which may be secondary to fluid retention.

**Central Nervous System**

*Common.* Headache, emotional lability, irritability, nervousness, anxiety, changes in appetite, depression.

*Rare.* Weakness, faintness, dizziness, vertigo, fatigue, tremor, benign intracranial hypertension.

*Very Rare.* Provocation of migraine, aggravation of epilepsy.

*Reported but Incidence Unknown.* Paraesthesias, sleep disorders, chills, cataracts, and rarely Guillain-Barre syndrome.

**Haematological**

*Rare.* Increased red cell and platelet count. Polycythemia, leucopenia, thrombocytopenia.

*Very Rare.* Reversible erythrocytosis and eosinophilia. Splenic peliosis.

*Reported but Incidence Unknown.* Leucocytosis.

**Cardiovascular**

*Rare.* Elevation in blood pressure and exacerbation of existing hypertension, palpitation and tachycardia. Thrombotic events have also been observed, including sagittal sinus and cerebrovascular thrombosis as well as arterial thrombosis. Cases of myocardial infarction have been reported.

**Ophthalmic**

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

**Other**

*Common.* Increased insulin requirements in diabetic patients, changes in libido, pelvic pain.

*Very Rare.* Epigastric pain, interstitial pneumonitis. Pleuritic pain.

*Reported but Incidence Unknown.* Bleeding gums, fever, Bartholin's cyst, and rarely nipple discharge.

**Dosage and Administration**

In women of reproductive age, therapy should begin during menstruation. A sensitive test (e.g. beta subunit test if available) capable of determining early pregnancy is recommended immediately prior to start of therapy to ensure the patient is not pregnant. Additionally, a non-hormonal method of contraception should always be used during danazol therapy (see **Precautions**).

*Endometriosis.* 200 to 800 mg danazol daily in two to four divided doses. It is recommended that treatment be initiated with a dosage of 800 mg daily in four divided doses. In some patients, it may be possible to maintain improvement with a reduced dosage once a satisfactory response has been obtained. Treatment should continue uninterrupted for 3 to 6 months, but may be extended to 9 months if necessary.

*Menorrhagia.* A course of 200 to 400 mg danazol daily in divided doses for up to 6 months. 200 mg is usually sufficient to reduce menstrual blood flow to acceptable limits.

*Hereditary Angioedema.* 200 to 600 mg danazol daily in divided doses. Dosage should be kept as low as possible with adjustment to meet individual patient requirements. Consideration should be given to interrupting treatment after an attack free period.

*Fibrocystic Breast Disease.* The minimum effective dose should be used. 200 mg daily is an effective dose in the majority of patients. In some instances, 400 mg/day may be warranted.

## Instructions to Patients

Advise female patients that ovulation and menses may cease. Patients should be advised that use of danazol during pregnancy may damage the foetus, and that if pregnancy is suspected, danazol should be stopped and a physician consulted. A non-hormonal method of contraception should be recommended. Therapy should begin during menstruation.

## Overdosage

Not reported in humans. LD<sub>50</sub> could not be determined in animals but danazol was found not to cause death after single oral doses from 5,000 mg/kg in rabbits and dogs, to 16,000 mg/kg in rats and mice.

*Symptoms.* Overdosage could reflect the adverse reactions seen with the drug, such as nausea, indigestion and oedema.

*Treatment.* General supportive measures; give diuretics if oedema occurs.

## Presentation and Storage Conditions

*Azol 100,* 100 mg capsule: light grey body with dark grey cap, marked G on the cap and DL100 on the body in black; bottles of 100.

*Azol 200,* 200 mg capsule: white body with orange cap, marked G on the cap and DL200 on the body in black; bottles of 100.

Store below 30°C.

## **Poison Schedule of the medicine**

S4 – Prescription Only Medicine

### **NAME AND ADDRESS OF THE SPONSOR**

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### **DATE OF APPROVAL**

*Approved by the Therapeutic Goods Administration on 21 June 2005.*