

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**74582**

**DRAFT FINAL PRINTED LABELING**

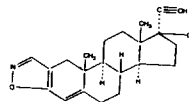
**APPROVED**

**DANAZOL CAPSULES, USP**  
Revised JUNE 1995  
88-836

**AUG 9 1996**

**DESCRIPTION:**

Danazol is a synthetic steroid derived from ethisterone. Chemically, danazol is 17 $\alpha$ -Pregna-2,4-dien-20-yno[2,3-d]-isoxazol-17-ol, which has the following structural formula:



$C_{27}H_{42}NO_2$  Molecular Weight: 374.66

Each capsule, for oral administration, contains 200 mg of danazol. In addition, each capsule contains the following inactive ingredients: lactose monohydrate, magnesium stearate, sodium starch glycolate, and stearic acid.

The capsule shell contains D&C red no. 28, D&C yellow no. 10, FD&C red no. 40, pectalin, silicon dioxide, sodium lauryl sulfate, and titanium dioxide.

The imprinting ink contains black iron oxide, D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, pharmaceutical glaze, and propylene glycol.

**CLINICAL PHARMACOLOGY:**

Danazol suppresses the pituitary-ovarian axis. This suppression is probably a combination of depressed hypothalamic-pituitary response to lowered estrogen 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).

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.

Bioavailability studies indicate that blood levels do not increase proportionally with increases in the administered dose. When the dose of danazol is doubled the increase in plasma levels is only about 35% to 40%.

Separate single dosing 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 three-to-four 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.

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 to 90 days when therapy with danazol is discontinued.

In the treatment of hereditary angioedema, danazol at effective doses prevents attacks of the disease characterized by episodic edema 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 angioedema 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.

#### **INDICATIONS AND USAGE:**

##### **Endometriosis:**

Danazol is indicated for the treatment of endometriosis amenable to hormonal management.

##### **Fibrocystic Breast Disease:**

Most cases of symptomatic fibrocystic breast disease may be treated by simple measures (e.g., padded brassieres and analgesics).

In infrequent patients, symptoms of pain and tenderness may be severe enough to warrant treatment by suppression of ovarian function. Danazol is usually effective in decreasing nodularity, pain, and tenderness. It should be stressed to the patient that this treatment is not innocuous in that it involves considerable alterations of hormone levels and that recurrence of symptoms is very common after cessation of therapy.

##### **Hereditary Angioedema:**

Danazol is indicated for the prevention of attacks of angioedema of all types (cutaneous, abdominal, laryngeal) in males and females.

#### **CONTRAINDICATIONS:**

Danazol should not be administered to patients with:

1. Undiagnosed abnormal genital bleeding.
2. Markedly impaired hepatic, renal, or cardiac function.
3. Pregnancy. (See **WARNINGS**).
4. Breast feeding.
5. Porphyria - Danazol can induce ALA synthetase activity and hence porphyrin metabolism.

**WARNINGS:**

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 nonhormonal 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 fetus. Exposure to danazol in utero may result in androgenic effects on the female fetus; reports of clitoral hypertrophy, labial fusion, urethral sinus defect, vaginal atresia, and ambiguous genitalia have been received. (See PRECAUTIONS: Pregnancy, Teratogenic Effects.)

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

Experience with long-term therapy with danazol is limited. Peliosis hepatis and benign hepatic adenoma have been observed with long-term use. Peliosis hepatis and hepatic adenoma may be silent until complicated by acute, potentially life-threatening intra-abdominal hemorrhage. 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 edema 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 pseudotumor cerebri. Early signs and symptoms of benign intracranial hypertension include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilledema and, if present, the patients should be advised to discontinue danazol immediately and be referred to a neurologist for further diagnosis and care.

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 prescribers 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.

Before initiating therapy of fibrocystic breast disease with danazol, carcinoma of the breast should be excluded. However, nodularity, pain, 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, carcinoma should be considered and ruled out.

Patients should be watched closely for signs of androgenic effects some of which may not be reversible even when drug administration is stopped.

(Over)

**PRECAUTIONS:**

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, require careful observation.

Since hepatic dysfunction manifested by modest increases in serum transaminase levels has been reported in patients treated with danazol, periodic liver function tests should be performed (see **WARNINGS** and **ADVERSE REACTIONS**).

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

**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.

**Laboratory Tests:**

Danazol treatment may interfere with laboratory determinations of testosterone, androstenedione and dehydroepiandrosterone.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

No valid studies have been performed to assess the carcinogenicity of danazol.

**Pregnancy, Teratogenic Effects: (See CONTRAINDICATIONS.)**

**Pregnancy Category X.** Danazol administered orally to pregnant rats from the 6th through the 15th day of gestation at doses up to 250 mg/kg/day (7-15 times the human dose) did not result in drug-induced embryotoxicity or teratogenicity, nor difference in litter size, viability or weight of offspring compared to controls. In rabbits, the administration of danazol on days 6-18 of gestation at doses of 60 mg/kg/day and above (2-4 times the human dose) resulted in inhibition of fetal development.

**Nursing Mothers:**

(See **CONTRAINDICATIONS**.)

**Pediatric Use:**

Safety and effectiveness in pediatric patients have not been established.

**ADVERSE REACTIONS:**

The following events have been reported in association with the use of danazol:

Androgen like effects include weight gain, acne and seborrhea. Mild hirsutism, edema, 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 include menstrual disturbances in the form of spotting, alteration of the timing of the cycle and amenorrhea. Although cyclical bleeding and ovulation usually return within 60-90 days after discontinuation of therapy with danazol, persistent amenorrhea has occasionally been reported.

Flushing, sweating, vaginal dryness and irritation and reduction in breast size, may reflect lowering of estrogen. Nervousness and emotional lability have been reported. In the male 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 have been reported. (See **WARNINGS** and **PRECAUTIONS**.)

Abnormalities in laboratory tests may occur during therapy with danazol including CPK, glucose tolerance, glucagon, thyroid binding globulin, sex hormone binding globulin, other plasma proteins, lipids and lipoproteins.

The following reactions have been reported, 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, paresthesias, weakness; visual disturbances, and rarely, benign intracranial hypertension, anxiety, changes in appetite, chills, and rarely convulsions, Guillain-Barre syndrome; *gastrointestinal*: gastroenteritis, nausea, vomiting, constipation, and rarely, pancreatitis; *musculoskeletal*: muscle cramps or spasms, or pains, joint pain, joint lockup, joint swelling, pain in back, neck, or extremities, and rarely, carpal tunnel syndrome which may be secondary to fluid retention; *genitourinary*: hematuria, prolonged post-therapy amenorrhea; *hematologic*: an increase in red cell and platelet count. Reversible erythrocytosis, leukocytosis or polycythemia may be provoked. Eosinophilia, leukopenia and thrombocytopenia have also been noted. *Skin*: rashes (maculopapular, vesicular, papular, purpuric, petechial), and rarely, sun sensitivity, Stevens-Johnson syndrome; *other*: increased insulin requirements in diabetic patients, change in libido, elevation in blood pressure, and rarely, cataracts, bleeding gums, fever, pelvic pain, nipple discharge. Malignant liver tumors have been reported in rare instances, after long-term use.

#### **DOSAGE AND ADMINISTRATION:**

##### **Endometriosis:**

In moderate to severe disease, or in patients infertile due to endometriosis, a starting dose of 800 mg given in two divided doses is recommended. Amenorrhea and rapid response to painful symptoms is best achieved at this dosage level. Gradual downward titration to a dose sufficient to maintain amenorrhea may be considered depending upon patient response. For mild cases, an initial daily dose of 200 mg to 400 mg given in two divided doses is recommended and may be adjusted depending on 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. (See CONTRAINDICATIONS and WARNINGS.) It is essential that therapy continue uninterrupted for 3 to 6 months if necessary. After termination of therapy, if symptoms recur, treatment can be reinstated.

##### **Fibrocystic Breast Disease:**

The total daily dosage of danazol for fibrocystic breast disease ranges from 100 mg to 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 nonhormonal 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 to 3 months. Usually elimination of nodularity requires 4 to 6 months of uninterrupted therapy. Regular menstrual patterns, irregular menstrual patterns, and amenorrhea each occur in approximately one-third of patients treated with 100 mg of danazol. Irregular menstrual patterns and amenorrhea are observed more frequently with higher doses. Clinical studies have demonstrated that 50% of patients may show evidence of recurrence of symptoms within one year. In this event, treatment may be reinstated.

**Hereditary Angioedema:**

The dosage requirements for continuous treatment of hereditary angioedema 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 favorable initial response is obtained in terms of prevention of episodes of edematous attacks, the proper continuing dosage should be determined by decreasing the dosage by 50% or less at intervals of one to three 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.

**HOW SUPPLIED:**

Danazol Capsules, USP are available as:

200 mg: Opaque orange cap/transparent orange body capsule.  
Imprinted with black ink **Barr**  
635. Available in bottles of:  
60 NDC 0555-0635-09  
100 NDC 0555-0635-02  
500 NDC 0555-0635-04

Dispense with a child-resistant closure in a well-closed container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86° F).

**CAUTION:** Federal law prohibits dispensing without prescription.

**MANUFACTURED BY**  
**BARR LABORATORIES, INC.**  
POMONA, NY 10970  
BR-635  
Revised JUNE 1995

**Usual Dosage:**

See package brochure.

Dispense with a child-resistant closure in a well-closed container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.

NDC 0555-0635-09

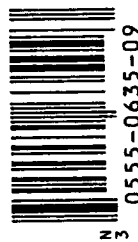


**Danazol  
Capsules, USP**

**200 mg**

Caution: Federal law prohibits dispensing without prescription.

**60 Capsules**



Exp. Date: **AUG 9 1996**  
Lot No.:

BARR LABORATORIES, INC.

Pomona, NY 10970

R6-95

BARR LABORATORIES, INC.

NDC 0555-0635-02

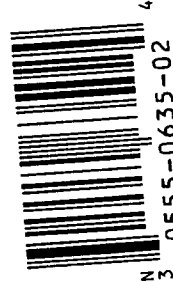


**Danazol  
Capsules, USP**

**200 mg**

Caution: Federal law prohibits dispensing without prescription.

**100 Capsules**



Exp. Date: **AUG 9 1996**  
Lot No.:

**Usual Dosage:**  
See package brochure.

Dispense with a child-resistant closure in a well-closed container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.  
Pomona, NY 10970

R6-95

**Usual Dosage:**

See package brochure.

Dispense with a child-resistant closure in a well-closed container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.  
Pomona, NY 10970

R6-95

BARR LABORATORIES, INC.

NDC 0555-0635-04



**Danazol  
Capsules, USP**

**200 mg**

Caution: Federal law prohibits dispensing without prescription.

**500 Capsules**



Exp. Date: **AUG 9 1996**  
Lot No.:

Exp. Date:  
Lot No.: