Danazol

CAS Number: 17230-88-5
Molecular Weight: 337.46 g/mol
Molecular Formula: C_{22}H_{27}NO_{2}
Systematic (IUPAC): (1S,2R,13R,14S,17R,18S)-17-ethynyl-2,18-dimethyl-7-oxa-6-azapentacyclo[11.7.0.0^{2,10}.0^{4,8}.0^{14,18}]icosa-4(8),5,9-trien-17-ol

**DRUG DESCRIPTION**
Danazol is a synthetic steroid derived from ethisterone. Chemically, Danazol is 17α-Pregna-2,4-dien-20-yno[2,3-d]-isoxazol-17-ol.

Each capsule, for oral administration, contains 50 mg, 100 mg or 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 yellow no. 10, gelatin, silicon dioxide, sodium lauryl sulfate, and titanium dioxide. The 50 mg and 100 mg capsule shells also contain FD&C yellow no. 6. The 200 mg capsule shell also contains FD&C red no. 40 and D&C red no. 28.

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.

This medication is a synthetic hormone. It is used to treat pain and infertility caused by endometriosis, a condition involving the tissue of the uterus. It is also used in the treatment of cysts or lumps in the breast or may be prescribed for heavy menstrual flow.

**DOSAGE**

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. It is essential that therapy continue uninterrupted for 3 to 6 months but may be extended to 9 months if necessary. After termination of therapy, if symptoms recur, treatment can be reinstituted.

**SIDE EFFECTS**

May cause dizziness, headache, fatigue, appetite changes, stomach upset, bloating, or anxiety. These effects should disappear as your body adjusts to the medication. Other side effects reported include oily skin, weight gain, flushing, changes in sleep patterns, change in sex drive, muscle cramps, chills, fluid retention in the hands or feet or nasal congestion. Notify your doctor if any of these become bothersome. Notify your doctor if you experience: depression, hot flashes, deepening of the voice, abnormal growth of fine body hair or facial hair, vision changes, yellowing of the eyes or skin, one-sided weakness, slurred speech. Women often experience no or irregular menstrual periods while taking this medication. Menstrual periods usually return within 90 days of stopping the drug. If you notice other effects not listed above, contact your doctor or pharmacist.

Androgenic side effects are of concern, because in sensitive female patients, danazol can enhance unwanted hair growth, leading to hirsutism. On rare occasion, it can deepen the voice. Other possible side effects include acne and oily skin. Because danazol is
metabolized by the liver, it cannot be used by patients with liver disease, and in patients receiving long-term therapy, liver function must be monitored on a periodic basis. Some patients who use danazol experience weight gain and fluid retention. Due to these limitations, danazol is seldom prescribed continuously beyond six months.

The use of danazol for endometriosis has been linked to an increased risk of ovarian cancer. Patients with endometriosis have specific risk factors for ovarian cancer so this may not apply for other uses. Danazol has, like most other androgenic agents, been linked with an increased risk of liver tumors.

**PRECAUTIONS**

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, urogenital sinus defect, vaginal atresia, and ambiguous genitalia have been received. (See PRECAUTIONS: Pregnancy, Teratogenic Effects.) Thromboembolism, thrombotic and thrombophlebitic 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.

**INTERACTION**

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 treatment may interfere with laboratory determinations of testosterone, androstenedione and dehydroepiandrosterone. No valid studies have been performed to assess the carcinogenicity of Danazol.

Tell your doctor or pharmacist if you are taking or planning to take any over-the-counter or prescription medications or dietary supplements while taking this drug. Drug doses may need to be modified or a different drug prescribed. The following drugs and drug classes interact with this drug:

- Carbamazepine
- Insulin
- Warfarin

**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.

CONSUMER INFORMATION
WARNING: This drug must not be used during pregnancy because its use may result in birth defects. In females, treatment should begin during menstruation. Otherwise, an early pregnancy test is recommended before starting treatment. Use a reliable, non-hormonal birth control method (e.g., diaphragm, condoms) while taking this drug. Consult your doctor for details.

Danazol may rarely cause serious (sometimes fatal) blood clots, liver disease (e.g., peliosis hepatis, hepatic adenoma), and increased pressure on the brain (pseudotumor cerebri, benign intracranial hypertension). Tell your doctor immediately if you have: weakness on one side of the body, slurred speech, vision changes, confusion, sudden stomach/abdominal pain or swelling, dark urine, persistent nausea/vomiting, yellowing eyes/skin, swollen eyes, unusual headache.

USES: This medication is used to treat several conditions, including pelvic pain and infertility due to a uterus condition (endometriosis), breast pain and tenderness due to nodules (fibrocystic breast disease), and swelling of the abdomen/arms/face/airway due to a certain congenital disease (hereditary angioedema).

Danazol is an androgen similar to testosterone. In women, it works by preventing the ovaries from producing certain natural substances (hormones) that
can make these conditions worse. In both men and women, it also works on the body's defense system (immune system) to correct the problems related to angioedema.

**MISSED DOSE:** If you miss a dose, take it as soon as you remember. If it is near the time of the next dose, skip the missed dose and resume your usual dosing schedule. Do not double the dose to catch up.

**STORAGE:** Store at room temperature away from light and moisture. Different brands require different storage temperatures, so consult your pharmacist for more information. Do not store in the bathroom. Keep all medicines away from children and pets.

**Type**
small molecule

**Description**
A synthetic steroid with antigonadotropic and anti-estrogenic activities that acts as an anterior pituitary suppressant by inhibiting the pituitary output of gonadotropins. It possesses some androgenic properties.

Danazol has been used in the treatment of endometriosis and some benign breast disorders.

**Categories**
Estrogen Antagonists

**Taxonomy**

**Kingdom**
Organic

**Classes**
Steroids and Steroid Derivatives

**Substructures**
Pharmacology

Indication
For the treatment of endometriosis and fibrocystic breast disease (in patients unresponsive to simple measures). Also used for the prophylactic treatment of all types of hereditary angioedema in males and females.

Pharmacodynamics
Danazol is a derivative of the synthetic steroid ethisterone, a modified testosterone. It was approved by the U.S. Food and Drug Administration (FDA) as the first drug to specifically treat endometriosis, but its role as a treatment for endometriosis has been largely replaced by the gonadotropin-releasing hormone (GnRH) agonists. Danazol has antigonadotropic and anti-estrogenic activities. Danazol acts as an anterior pituitary suppressant by inhibiting the pituitary output of gonadotropins. It possesses some androgenic properties.

Mechanism of Action
As a gonadotropin inhibitor, danazol suppresses the pituitary-ovarian axis possibly by inhibiting the output of pituitary gonadotropins. Danazol also depresses the
preovulatory surge in output of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), thereby reducing ovarian estrogen production. Danazol may also directly inhibit ovarian steroidogenesis; bind to androgen, progesterone, and glucocorticoid receptors; bind to sex-hormone-binding globulin and corticosteroid-binding globulin; and increases the metabolic clearance rate of progesterone. Another mechanism of action by which danazol may use to facilitate regression of endometriosis is by decreasing IgG, IgM, and IgA concentrations, as well as phospholipid and IgG isotope autoantibodies. In the treatment of endometriosis, as a consequence of suppression of ovarian function, danazol causes both normal and ectopic endometrial tissues to become inactive and atrophic. This leads to anovulation and associated amenorrhea. In fibrocystic breast disease, the exact mechanism of action of danazol is unknown, but may be related to suppressed estrogenic stimulation as a result of decreased ovarian production of estrogen. A direct effect on steroid receptor sites in breast tissue is also possible. This leads to a disappearance of nodularity, relief of pain and tenderness, and possibly changes in the menstrual pattern. In terms of hereditary angioedema, danazol corrects the underlying biochemical deficiency by increasing serum concentrations of the deficient C1 esterase inhibitor, resulting in increased serum concentrations of the C4 component of the complement system.

**Metabolism**

Hepatic, to principal metabolites, ethisterone and 17-hydroxymethylethisterone.
Affected organisms
Humans and other mammals

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