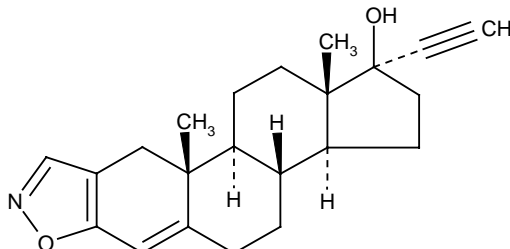


PRODUCT INFORMATION

DANOCRINE

DESCRIPTION

Danazol is a synthetic hormone derived from ethisterone. Chemically it is 17α -pregna-2,4-dien-20-yno(2,3-d)isoxazol-17 β -ol, a white or pale yellow crystalline powder, which has the following structural formula:



MOLECULAR WEIGHT: 337.5

CAS Number: 17230-88-5

It is practically insoluble in water, but soluble in chloroform and in acetone. It has a melting point of 225°C with some decomposition

The excipients contained in Danocrine are: lactose, maize starch, purified talc, magnesium stearate, titanium dioxide, gelatin.

PHARMACOLOGY

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%.

The 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 using radio-labelled danazol have demonstrated the continued presence of radioactivity in the intestines and stomach suggesting that danazol and its metabolites may undergo enterohepatic circulation. No consistent localisation of radioactivity has been found in any tissue other than the adrenal gland and the organs of excretion.

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.

In humans the major urinary metabolites of danazol are 2-hydroxymethylethisterone and ethisterone. Other minor urinary metabolites identified are Δ -2-hydroxymethylethisterone, 6 β -hydroxy-2-hydroxymethylethisterone and Δ -6 β -hydroxy-2-hydroxymethylethisterone. None of these metabolites have been found to exhibit antigonadotrophic activity.

Pharmacological Action

Endometriosis and Menorrhagia

In women of reproductive age, DANOCRINE 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.

DANOCRINE depresses the output of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

In the treatment of endometriosis, DANOCRINE 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 DANOCRINE on the pituitary-ovarian axis.

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

Generally the pituitary-suppressive action of DANOCRINE is reversible. When DANOCRINE 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 C₁ esterase inhibitor activity. DANOCRINE administration results in increased levels of C₁ 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 C₄ also increase during DANOCRINE administration, frequently rising to the normal range.

Levels of albumin, C₃ and α -macroglobulin show no statistically significant changes with DANOCRINE therapy; no increase in total serum protein occurs.

The mechanism by which DANOCRINE increases the levels of C₁ esterase inhibitor activity and C₄ is unknown at present.

Fibrocystic Breast Disease

DANOCRINE suppresses the ovulatory luteinizing surge, interferes with gonadal steroidogenesis (directly and indirectly) and dampens the gonadotrophin response to luteinizing hormone.

Clinical Experience

Endometriosis and Menorrhagia

Clinically, the action of DANOCRINE 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 DANOCRINE; in cases where it has been examined, this bleeding was associated with an atrophic endometrium.

DANOCRINE 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 DANOCRINE therapy.

Clinical studies have demonstrated the efficacy of DANOCRINE in the short-term management of menorrhagia. The reduction in blood loss continued for up to three 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 DANOCRINE 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 DANOCRINE courses.

DANOCRINE effectively prevents attacks in HAE and acts to correct the associated biochemical abnormality.

Fibrocystic Breast Disease

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

INDICATIONS

Endometriosis

DANOCRINE is indicated for use in the treatment of visually proven (e.g., laparoscopy) endometriosis where the required end-point of treatment is fertility, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Menorrhagia

DANOCRINE is indicated for the short-term (up to 6 months) management of intractable primary menorrhagia.

Hereditary Angioedema

DANOCRINE is indicated for the prophylaxis of attacks of hereditary angioedema of a severe or life-threatening nature, in male and female patients.

Fibrocystic Breast Disease

DANOCRINE is indicated for the 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

DANOCRINE is contraindicated in patients with:

1. Undiagnosed abnormal genital bleeding.
2. Undiagnosed ovarian/uterine masses.
3. Past jaundice with oral contraceptives.
4. Markedly impaired liver, renal or cardiac function, including oedema.
5. Pelvic infection.
6. Neoplasia of primary or secondary sexual organs.

7. Hypertension WHO II or worse.
8. Known hypersensitivity to danazol.
9. Pregnancy.
10. Breast feeding.
11. Porphyrria - Danocrine can induce ALA synthetase activity and hence porphyrin metabolism.
12. Androgen-dependant tumour.
13. Active thrombosis, thromboembolic disease or history of such events.

(see **WARNINGS**)

WARNINGS

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 intraabdominal haemorrhage. The physician should therefore 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 is stopped. Specific caution should be exercised when considering the use of Danocrine in professional singers.

Danazol should be stopped if there is evidence of virilization (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 pretreatment levels.

Patients taking DANOCRINE 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 treatment initiation, 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 DANOCRINE.

Use in Pregnancy (D)

Danazol inhibits ovulation in many women but pregnancies can occur if barrier contraception is not used. Virilization 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 therapy should commence during menstruation. 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. If a patient suspects she has become pregnant during treatment, she should cease danazol treatment 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.

Use During 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 nursing mothers.

Paediatric Use

Safety and efficacy in children have not been established.

PRECAUTIONS

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 isolated increases in serum transaminase levels and/or jaundice has been reported in patients treated with DANOCRINE, periodic liver function tests and close clinical monitoring should be performed. (See WARNINGS and ADVERSE REACTIONS).

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.*

Drug Interactions

Warfarin

Prolongation of prothrombin time occurs in patients stabilised on warfarin.

Anticonvulsant Therapy

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.*

Laboratory Tests

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

Instructions to be Given to Female Patients

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

ADVERSE REACTIONS

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

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 WARNINGS)

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 - 90 days after discontinuation of DANOCRINE, persistent amenorrhoea has occasionally been reported.
- Flushing (6%), vaginal dryness and irritation (4%) and sweating (3%) 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 have been reported in patients receiving a daily dosage of DANOCRINE of 400mg or more.

Rare

- Cholestatic jaundice
- Hepatic adenoma

Very rare

- Peliosis hepatis
- 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 SGOT, decreased PBI, blunted cyclical surges of LH, and induction of aminolevulinic acid (ALA) synthetase.
- Other events include reduction in thyroid binding globulin and T4, with increased uptake of T3 but without disturbance of thyroid stimulating hormone or of free thyroxine index.
- Total cholesterol and LDL cholesterol may increase and HDL cholesterol may decrease. A decrease in apolipoproteins AI and AII has been reported. (See WARNINGS).

The following reactions have also been reported:

Allergic

- Uncommonly urticaria and pruritis and rarely nasal congestion;

Skin

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 and 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.

CNS

Common

- headache, emotional lability, irritability, nervousness, anxiety, changes in appetite and depression.

Rare

- weakness, faintness, dizziness, vertigo, fatigue, tremor and benign intracranial hypertension.

Very rare

- provocation of migraine.
- aggravation of epilepsy.

Reported but incidence unknown

- Paraesthesias, sleep disorders, chills, cataracts and rarely Guillian-Barre Syndrome.

Haematologic

Rare

- Increased red cell and platelet count.
- polycythemia, leucopenia and 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 and pelvic pain.

Very rare

- Epigastric pain, interstitial pneumonitis
- Pleuritic pain

Reported but incidence unknown

- bleeding gums, fever, and Bartholin's cyst and rarely nipple discharge

Note	<i>very common</i>	$\geq 1/10$ ($\geq 10\%$)
	<i>common</i>	$\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$)
	<i>uncommon</i>	$\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1.0\%$)
	<i>rare</i>	$\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$)
	<i>very rare</i>	$< 1/10,000$ ($< 0.01\%$)

DOSAGE AND ADMINISTRATION

In women of reproductive age, therapy should begin during menstruation. A sensitive test (eg. 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 always be used during DANOCRINE therapy (See **WARNINGS**).

Endometriosis

200-800 mg danazol daily in two to four divided doses. It is recommended that treatment be initiated with a dosage of 800 mg daily in 4 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 200-400 mg danazol daily in divided doses for up to 6 months. 200 mg is usually sufficient to reduce menstrual blood flow to acceptable limits.

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.

Hereditary Angioedema

200-600 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.

OVERDOSAGE

Not reported in man. LD 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.

Clinical Features

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

Management

General supportive measures; give diuretics if oedema occurs.

PRESENTATION

200 mg capsules (white, marked with black D200 on body and cap): blister packs of 100.

100 mg capsules (white, marked with black D100 on body and cap): blister packs of 100.

100 mg capsules (white, marked with black D100 on body and cap): bottle of 100.

Store below 30°C.

POISONS SCHEDULE

Prescription Only Medicine

Sanofi-Synthelabo Australia Pty Limited
16 Byfield Street
North Ryde NSW 2113

Latest TGA Amendment: 5th July 1993.

Safety Related Notification: 20 June 2002

*Clinically significant change

Danocrine is a registered trademark