PRODUCT MONOGRAPH

[Pr] CYCLOMEN®
(danazol capsules, USP)

50mg, 100mg, 200mg Capsules

Pituitary Gonadotropin Inhibitor

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PRODUCT MONOGRAPH

Pr Cyclomen®
(danazol capsules, USP)

THERAPEUTIC CLASSIFICATION

Pituitary gonadotropin inhibitor

ACTIONS AND CLINICAL PHARMACOLOGY

In women of reproductive age, the primary mode of action of Cyclomen (danazol) is believed to be by suppression of the pituitary-ovarian axis, and inhibition of the output of gonadotropins from the pituitary gland.

Other mechanisms of action currently postulated to explain its effects are: 1) inhibition of midcycle FSH and LH surges; 2) inhibition of enzymes required for gonadal hormone synthesis; and 3) competitive binding of danazol to steroid receptors at target organs.

Danazol may also inhibit cyclic AMP accumulation in granulosa and luteal cells in response to gonadotrophic hormones. A wide range of actions on plasma proteins including increasing prothrombin, plasminogen, antithrombin III, alpha-2-macroglobulin, C1 esterase inhibitor, erythropoietin and reducing fibrinogen, thyroid binding and sex hormone binding globulins has been observed. Danazol increases the proportion and concentration of testosterone carried unbound in the plasma.

In postmenopausal women, danazol suppresses FSH and LH levels. It has a weak dose-related androgenic activity. Danazol is a weak androgen but anti-androgenic, progestogenic, anti-progestogenic, estrogenic and anti-estrogenic actions have also been observed.

Following oral administration in healthy adult females, danazol displays dose dependent absorption, which approaches linearity over the dosage range 100 to 400 mg twice daily in multiple dosing. Absorption is affected by prandial state, being approximately doubled if danazol is taken just after, compared with two hours before, a meal. The principal metabolites of danazol appear to be ethisterone and 17-hydroxymethylethisterone. The mean plasma elimination half-life of danazol is in the order of 24 hours.

Bioavailability studies indicate that blood levels do not increase proportionally with increases in the administered dose. When the dose of Cyclomen is doubled the increase in plasma levels is only about 35% to 40%.
When used for the treatment of endometriosis, danazol alters the endometrium so that it becomes inactive and atrophic. (Dmowski and Greenblatt 1971, Greenblatt et al. 1971, Greenblatt 1972, Child and Tan 2001). Danazol produces marked regression of ectopic endometrial tissue.

(Friedlander 1973). Pre- and post-medication laparoscopy was done on 96 subjects. Complete or partial resolution of ectopic endometrial sites was found in 85 out of 88 patients (97%) receiving 800 mg danazol daily and in 6 out of 8 patients receiving 600 mg. This regression is due to the suppression of ovarian function which results in anovulation and associated amenorrhea. Changes in vaginal cytology and cervical mucus reflect the suppressive effect of danazol on gonadal steroid action and were found in 75% of 116 patients.

After institution of therapy with danazol, patients (generally) have one additional menstrual period and then become anovulatory and amenorrheic, though some patients have occasional spotting or bleeding for the duration of treatment. (Lauersen et al. 1975, Young and Blackmore 1977). In cases where it has been examined, this bleeding was associated with an atrophic endometrium. On regimens of between 200 and 600 mg daily for 3 to 6 months, highly effective relief of the signs and symptoms of endometriosis was obtained. Complete or partial relief of dysmenorrhea occurred in 290/309 patients (94%), of pelvic pain in 276/322 (85%), of dyspareunia in 134/160 (84%) and of induration of the cul-de-sac in 217/274 (79%). Dysmenorrhea and pelvic pain are usually relieved within the first few weeks after initiation of therapy; relief of dyspareunia and induration of the cul-de-sac take somewhat longer (Lauersen et al. 1975).

Generally, the action of danazol on hormonal regulation is reversible. Ovulation and predictable cyclical bleeding usually return within 60 to 90 days when danazol therapy is discontinued. Discontinuation results in a rebound in FSH and LH secretion with consequent increase in fecundity. (Greenblatt et al. 1974, Goebel and Rjosk 1977, Young and Blackmore 1977).

In the treatment of fibrocystic breast disease, the mode of action of danazol on the breasts is not known. Therapy with this drug lasting up to 6 months, however, results in relief of pain, tenderness and various degrees of regression of nodularity (Millet and Dirbas, 2002). An alteration or improvement of the pathological process at the tissue level has not been demonstrated.

Oligomenorrhea and amenorrhea occur in a dose-dependent manner in most patients. Generally however, the action of danazol on hormonal regulation is reversible and normal menstrual patterns return within two (2) months following discontinuation of therapy.

INDICATIONS AND CLINICAL USE

Endometriosis:
Cyclomen (danazol) is indicated for the treatment of endometriosis associated symptoms and/or to reduce the extent of endometriotic foci. Cyclomen may be used either in conjunction with surgery or, as sole hormonal therapy, in patients not responding to other treatments.

Benign Fibrocystic Breast Disease:
Cyclomen (danazol) is indicated for the symptomatic relief of severe pain and tenderness associated with fibrocystic disease of the breast. Cyclomen should be used in those patients who do not obtain adequate relief through other therapeutic measures or in whom such measures are otherwise inadvisable.

Carcinoma of the breast should be excluded prior to commencing treatment.

The treatment course should be limited to three to six months maximum.

CONTRAINDICATIONS

Cyclomen (danazol) is contraindicated in patients presenting with:

1) undiagnosed abnormal genital bleeding;
2) genital neoplasia;
3) markedly impaired hepatic, renal or cardiac function;
4) pregnancy (see WARNINGS) ;
5) breast feeding;
6) porphyria - Cyclomen can induce ALA synthetase activity and should not be used in patients with known or suspected acute intermittent porphyria;
7) androgen-dependent tumor;
8) active thrombosis or thromboembolic disease and history of such events.
9) known hypersensitivity to danazol or to any ingredient in the formulation (for a complete list, see CHEMISTRY section)~~;~~
10) concomitant administration with simvastatin (see PRECAUTIONS)

WARNINGS

Cyclomen (danazol) may cause fetal harm when administered to a pregnant woman. Exposure to danazol in utero may result in androgenic effects on the female fetus, comprising to date clitoral hypertrophy, labial fusion, urogenital sinus defect, vaginal atresia, and ambiguous genitalia. A sensitive test (eg. beta subunit test if available) capable of determining early pregnancy is recommended immediately prior to start of therapy. Additionally, danazol should be initiated during menstruation and an effective nonhormonal method of contraception should be used

during therapy. If a patient becomes pregnant while taking Cyclomen, administration of the drug should be discontinued and the patient should be apprised of the potential risk to the fetus.

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

Before initiating therapy of fibrocystic breast disease with Cyclomen, carcinoma of the breast should be excluded.

Nodularity, pain and tenderness due to fibrocystic breast disease may prevent recognition of underlying carcinoma before treatment is begun (Baker 1979). As evidenced during clinical trials with Cyclomen, breast pain and tenderness are usually significantly relieved by the first month of treatment and eliminated in 2 to 3 months. Regression of nodularity may require up to 6 months of uninterrupted therapy (Blackmore 1977). Therefore, if any nodule persists or enlarges during treatment, carcinoma should be considered and ruled out (Asch and Greenblatt 1977, Aksu et al. 1978).

Attempts should be made to determine the lowest clinically effective dose. In view of the fact that some cases of endometriosis may be resistant to one specific form of hormone therapy and responsive to another, Cyclomen may prove to be of benefit in such cases. There are some limited data in support of the use of Cyclomen in therapy-resistant cases of this type (Greenblatt 1974).

Cyclomen should be stopped if any clinically significant adverse event arises, and particularly if there is evidence of:

- virilization. Patients should be watched closely for signs of virilization. Some of these, in rare cases (such as deepening of voice, clitoral hypertrophy and more than minimal hirsutism), may not be reversible. In these cases, cessation of therapy should be considered in order to prevent further progression due to the risk of irreversible androgenic effects.
- papilledema, headache, visual disturbances or other signs or symptoms of raised intracranial pressure,
- jaundice or other indication of significant hepatic disturbance. Patients should be advised to immediately report symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching).
- thrombosis or thromboembolism.

It should be stressed to the patient that danazol treatment involves considerable alterations of hormone levels which may be evidenced by such side effects as the occurrence of acne, weight gain, irregular menstrual patterns or amenorrhea, signs of virilization, and that recurrence of the initial symptoms may occur following cessation of therapy.

Experience with danazol greater than six months is limited. While 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. Therapy with other steroids alkylated at the 17 position has been associated with serious toxicity (cholestatic jaundice, peliosis hepatis, benign hepatic adenomata, hepatocellular focal nodular hyperplasia, malignant hepatic tumors). The physician therefore should be alerted to the possibility that similar toxicity may develop during therapy with danazol, especially when administration is continued beyond recommended time periods. Peliosis hepatis and hepatic adenoma may be silent until complicated by acute potentially life threatening intra abdominal hemorrhage. Cases of hepatocellular liver injury, including life-threatening hepatic failure, and hepatocellular jaundice have been reported in patients treated with danazol in the post-marketing setting (see ADVERSE REACTIONS).

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 endometriosis-treated patients. (Ness 2003)

Extremely rare cases of serious adverse events and death have been reported in individual patients who were taking danazol, however, a causal relationship to the administration of danazol has neither been confirmed nor refuted. These included one case of acute leukemia, one fatal case of primary liver carcinoma, and a few cases of peliosis and hepatomas and the association of danazol with several cases of benign hepatic adenoma, malignant hepatic tumors (Cofavreux et al. 2001) benign intracranial hypertension (pseudotumor cerebri), thromboembolism, thrombotic and thrombophlebitic events, including sagittal sinus thrombosis and life-threatening or fatal strokes.

PRECAUTIONS

In view of its pharmacology, known interactions and side effects, particular care should be observed in using danazol in those with hepatic or renal disease; hypertension or other cardiovascular disease; any state which may be exacerbated by fluid retention; diabetes mellitus; polycythemia; epilepsy; lipoprotein disorder; a history of thrombosis or thromboembolic disease; a history of marked or persistent androgenic reaction to previous gonadal steroid therapy; migraine (see below for further precautions on several of these conditions).

The treatment course should be limited to three to six months maximum.

Danazol may cause erratic results in thyroid function tests (Pannall and Mass 1977, Thorell et al. 1979, Barbieri 1980, Graham and Gambrell 1980). Patients who are taking danazol have shown the uncommon combination of low or low-normal serum thyroxine, much reduced thyroxine-binding globulin and normal free thyroxine index (Pannall and Mass 1977, Barbieri 1980). In men and women a dose of 600 mg danazol daily for 15 days has been shown to have

no significant effect on basal levels of TSH or on its response to thyrotrophin-releasing hormone (Franchimont and Cramilion 1977).

The finding of normal thyroid-stimulating hormone levels and free thyroxine index during danazol therapy indicates that patients are euthyroid. It is believed that the abnormality of thyroid function tests is due to an androgen-like reduction in thyroxine-binding globulin rather than a true decrease in thyroid function or interference with the pituitary-thyroid axis (Graham and Gambrell 1980).

Changes in plasma levels of several other proteins have been observed during danazol administration. Pre-albumin, C1-esterase inhibitor, haptoglobins, transferrin, antithrombin III, prothrombin and plasminogen were all shown to increase following administration of danazol. The concentrations of T_4-binding globulin, pregnancy zone protein and sex hormone-binding globulin decreased to one-third or less on administration of danazol. Uptake of T_3 was increased. The plasma estradiol content fell correspondingly (Laurell and Rannevik 1979). The clinical significance of these changes has not yet been determined.

A temporary alteration of lipoproteins in the form of decreased high density lipoproteins and possibly increased low density lipoproteins has been reported in some patients during Cyclomen therapy. Prescribers should consider the possible risk of atherosclerosis and coronary artery disease versus the benefit of therapy.

Since hepatic and hematologic dysfunction has been reported in patients treated with Cyclomen, periodic liver function tests and hematological tests should be performed (see Adverse Reactions section).

For repeated courses of treatment, biannual hepatic ultrasonography is recommended.

Fatal cases of fulminant hepatitis have been reported in three patients while on danazol therapy. One of these patients was shown to have an infection with hepatitis B virus while the symptoms and clinical course of the other two patients were consistent with non A - non B hepatitis.

If faced with continuing abnormalities of biochemical tests and/or their corresponding clinical manifestations, the possible risks should be carefully weighed against the potential benefits and discontinuation of danazol treatment should be considered.

It may be prudent to continue non-hormonal contraception after danazol treatment for fibrocystic breast disease until a menstrual period that is normal in amount of flow and duration has occurred.

Cyclomen may potentiate the effects of coumadin-type anticoagulants.

In cases where such drugs are given concurrently with Cyclomen, careful attention to and, if necessary, readjustment of, their dosages is recommended.

Danazol can increase the plasma level of carbamazepine and may affect responsiveness to this agent and to phenytoin. A similar interaction with phenobarbital is likely.

Plasma concentrations of cyclosporin and tacrolimus administered concurrently with danazol may be higher than expected leading to an increase of the renal toxicity of these drugs. Elevated plasma glucagon levels have been reported in a few patients receiving danazol; diabetic patients on insulin or oral hypoglycemic agents may need to have the dosage of those agents increased appropriately in order to maintain euglycemia as danazol can cause insulin resistance.

Danazol can diminish the effectiveness of antihypertensive agents and likely interact with gonadal steroid therapy.

Danazol can increase the calcemic response to alpha calcidol in primary hypoparathyroidism.

Alteration in values for laboratory tests may occur during danazol therapy including CPK, glucose tolerance, glucagon, thyroid binding globulin, sex hormone binding globulin, other plasma proteins, lipid and lipoproteins and urinary 17-ketosteroids.

Statins: The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with statins metabolized by CYP3A4 such as simvastatin, atorvastatin and lovastatin. The concomitant administration of danazol with simvastatin is contraindicated (see CONTRAINDICATIONS).

Pregnancy: (See WARNINGS and CONTRAINDICATIONS).

Nursing Mothers: (See WARNINGS and CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children have not been established.

Ability to Drive and Use Machines: Danazol is unlikely to affect the ability to drive or use machines.

ADVERSE REACTIONS

Any of the following adverse effects can occur in patients receiving danazol: acne, edema (facial), mild hirsutism, decrease in breast size, deepening of the voice, oiliness of the skin or hair, weight gain, seborrhea, and rarely, clitoral hypertrophy.

Also hypoestrogenic manifestations such as flushing, sweating, vaginitis including itching, dryness, burning and vaginal bleeding, nervousness and emotional lability have been reported.

Hepatic dysfunction, as evidenced by reversible elevated serum enzymes has been reported.

Cholestatic jaundice has been reported rarely. It is recommended that patients receiving Cyclomen be monitored for hepatic dysfunction by laboratory tests and clinical observation (See PRECAUTIONS). Rare occurrences of benign hepatic adenomata, malignant hepatic tumor and peliosis hepatis have also been observed with long-term use (> 6 months). Cases of hepatocellular injury, hepatic failure, hepatocellular jaundice and hepatocellular focal nodular hyperplasia have been reported.

Rare cases of pancreatitis have also been reported.

Although the following reactions have also been reported, a causal relationship to the administration of Cyclomen has neither been confirmed nor refuted:

allergic: urticaria, pruritus, rarely nasal congestion;

skin and mucous membranes: rashes (maculopapular, vesicular, papular, purpuric, petechial), acne, hyperpigmentation, hair loss, inflammatory erythematous nodules, altered skin pigmentation, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome and rarely sun sensitivity;

gastrointestinal: nausea, vomiting, constipation, gastroenteritis and rarely pancreatitis;

genitourinary: hematuria, prolonged post-therapy amenorrhea, disturbance of the menstrual cycle, intermenstrual spotting and/or prolonged anovulation;

musculoskeletal: muscle cramps or spasms, sometimes with elevation of creatine phosphokinase levels, muscle or joint pain, joint lock-up, joint swelling, pain in back, neck or extremities, fasciculation, limb pain and rarely carpal tunnel syndrome;

cardiovascular: exacerbation of hypertension, palpitation, 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;

CNS: headache, nervousness and emotional lability, dizziness and fainting, vertigo, depression, fatigue, chills, paresthesias, visual disturbances including visual hallucination followed by seizure, papilledema, retrobulbar neuritis, and rarely benign intracranial hypertension (pseudotumor cerebri), anxiety, sleep disorders, tremor, weakness, changes in appetite (including increased appetite), aggravation of epilepsy, provocation of migraine and Guillain Barre syndrome;

ophthalmic: visual disturbances such as blurring of vision, difficulty in focusing, difficulty in wearing contact lenses and need for temporary alteration in refractive correction;

hematologic: an increase in red cell and platelet count, thrombocytopenia, leukopenia and rarely eosinophilia, splenic peliosis, leukocytosis or polycythemia, thrombophlebitis;

other: hyperglucagonemia, increased insulin requirements in diabetic patients, decrease in HDL cholesterol affecting all subfractions, increase in LDL cholesterol levels with variable changes in total cholesterol, decrease in apolipoproteins Al and All (the clinical significance of these changes is not established); induction of aminolevulinic acid (ALA) synthetase, changes in libido, elevation in blood pressure, and rarely nipple discharge, cataracts, bleeding gums, fever, pelvic pain, epigastric and pleuritic pain, interstitial pneumonitis; fluid retention. Also, very rarely, reduction of spermatogenesis.

OVERDOSAGE

Available evidence suggests that acute overdosage would be unlikely to give rise to immediate serious reaction. Nonetheless, consideration should be given to removal of the drug by emesis or stomach pump, or to reduce the absorption of the drug by activated charcoal, and the patient should be kept under observation in case of any delayed reactions.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Danazol is for oral administration only.

Danazol should be given as a continuous course, 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.

Therapy should begin during menstruation. Otherwise, appropriate tests should be performed to ensure that the patient is not pregnant while on Cyclomen (danazol) therapy. An effective non-hormonal method of contraception should be used during the complete course of therapy. Regular menstrual patterns, irregular menstrual patterns and amenorrhea each occur in approximately one-third of patients treated with 100 mg of Cyclomen. Irregular menstrual patterns and amenorrhea are observed more frequently with higher doses.

The treatment course should be limited to three to six months maximum.

Endometriosis:
Clinical effectiveness has been achieved with total daily doses of Cyclomen ranging from 200 to 800 mg in two to four divided doses and administered without interruption for 3 to 6 months. If at the lower doses, an anovulatory and amenorrheic state is not achieved and if the symptomatology is not relieved in 30 to 60 days, the dose should be increased. In patients with severe presenting symptomatology, the usual starting dose is 800 mg daily. The maximum recommended daily dose is 800 mg. It is essential that therapy continue uninterrupted for 3 to 6 months. Shorter courses of therapy have been used as adjuncts to surgery. After termination of therapy, if symptoms recur, treatment can be reinstated.

Fibrocystic Breast Disease:
The total daily dose of Cyclomen ranges from 100 to 400 mg given in two divided doses depending upon patient response. Pain and tenderness usually respond to treatment after 30-40 days. Nodularity usually does not begin to regress until 60- 90 days after initiation of therapy. Treatment should continue uninterrupted until complete disappearance of symptoms or for six months, whichever occurs first. Clinical studies have demonstrated that approximately 50% of patients may show evidence of recurrence of symptoms within one year. In this event, treatment may be reinstated.

STORAGE AND STABILITY

Store at 15-30ºC, in a dry place.

AVAILABILITY

Cyclomen (danazol) is available in blisters as follows:

Hard pink gelatin capsules containing 50 mg of danazol, with “D50" on the cap and on the body; blisters of 100.

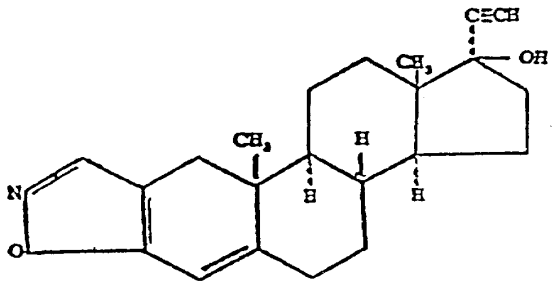
Hard bicolour (grey cap/white body) gelatin capsules containing 100 mg of danazol, with "D100" on the cap and on the body; blisters of 100.

Hard bicolour (orange cap/white body) gelatin capsules containing 200 mg of danazol with “D200” on the cap and on the body; blisters of 100.

Cyclomen is a Schedule F drug.

CHEMISTRY

Danazol is a synthetic steroid derived from ethisterone. It is a white to pale yellow, crystalline powder with a melting point of about 225°C with some decomposition, and has the following structural formula:



Molecular Formula: $C_{22}H_{27}NO_2$

Molecular Weight: 337.5

Chemical Name: 17α-pregna-2, 4-dien-20-yno[2,3,-d]-isoxazol-17-ol.

Composition:

50 mg Capsules: Each capsule contains 50 mg danazol and as non-medicinal ingredients, maize starch, red iron oxide, gelatin, lactose monohydrate, magnesium stearate, talc and titanium dioxide.

100 mg Capsules: Each capsule contains 100 mg danazol and as non-medicinal ingredients, maize starch, black iron oxide, gelatin, lactose monohydrate, magnesium stearate, talc and titanium dioxide.

200 mg Capsules: Each capsule contains 200 mg danazol and as non-medicinal ingredients, maize starch, red iron oxide, yellow iron oxide, gelatin, lactose monohydrate, magnesium stearate, talc and titanium dioxide.

PHARMACOLOGY

Pharmacology in Animals:
Laboratory studies have shown danazol to have marked pituitary gonadotropin inhibitory activity without overt sex hormonal activity when administered orally in a variety of bio-assays. Danazol was shown to have no estrogenic or progestational activity and to possess minimal, impeded androgenic activity. *In vitro* experiments have shown that danazol inhibits the biosynthesis of progesterone and estradiol-17β by cultured porcine granulosa cells and of progesterone by cultured porcine luteal cells (Tsang et al. 1979). This inhibition of steroidogenesis by danazol has further been shown to involve a step distal to gonadotropin-receptor interaction and adenosine- 3',5'-cyclic monophosphate formation (Menon et al. 1980), most likely by inhibiting enzymes involved in steroid biosynthesis (Barbieri et al. 1977, Tsang et al. 1979).

Pituitary inhibitory activity has been demonstrated in female rats and rhesus monkeys and in male rats. In reproductively mature female rats, danazol given daily for 2 weeks orally, produced a dose-related reduction in ovarian weights and a reduction in the percentage of vaginal estrus days.

Subcutaneous or oral administration daily for 2 weeks inhibited compensatory ovarian hypertrophy in unilaterally ovariectomized female rats. Daily oral administration to mature, regularly cycling female rhesus monkeys beginning on day 1 of the menstrual cycle produced a dose-related reduction in the number of monkeys which menstruated and in the number of menstrual cycles which occurred during treatment. Danazol was active orally in preventing pregnancy in mated female rats at dose levels which inhibit pituitary function and was an effective oral contraceptive in the female rhesus monkey when administered at 200 or 400 mg daily.

In intact male rats, danazol reduced the weight of the testes, ventral prostate and seminal vesicles in short-term medication studies (2 weeks) and when medication was given orally up to one year. In castrated or hypophysectomized male rats, danazol administered orally showed minimal androgenic activity. When administered concurrently with androgens or gonadotropin, danazol inhibited the stimulatory action of high dosage levels of these agents but did not inhibit the effects of lower doses of androgens.

Lack of Estrogenic Effects:
Danazol produced a shallow dose-related increase in the weight of the uterus when administered orally to immature female rats over a dose range of 3.12 to 800 mg/kg/day x 3. The uterine response was typical of that produced by an androgen. Danazol did not produce cornification of the vaginal epithelium when administered to ovariectomized female rats over a dose range of 20 to 1200 mg/kg/day x 2. When given orally alone to ovariectomized rhesus monkeys for 20 days at doses as high as 800 mg/kg, danazol did not produce estrogen-like withdrawal bleeding.

Lack of Oral Progestational Activity:

Danazol was not progestational when administered orally to immature female rabbits in doses up to 800 mg/kg/day x 5 (Clauberg assay). Danazol exhibited dose-related anti-progestational activity in the rabbit by inhibiting the endometrial response of concurrently administered progesterone. The administration of danazol concurrently with mestranol to ovariectomized rhesus monkeys did not modify the withdrawal bleeding pattern compared with that following mestranol treatment alone, indicating a lack of progestational activity.

Evaluation of Androgenic/Anabolic Effects:
Oral administration of danazol to castrated male rats produced minimal stimulation of the ventral prostate and seminal vesicles and a dose-related increase in the weight of the levator ani muscle. A high myotrophic to androgenic ratio was observed in a one-year study in which danazol was administered daily at 80 mg/kg. Danazol did not produce a masculinizing effect in pregnant female rats though it inhibited estrogen-induced withdrawal bleeding in ovariectomized rhesus monkeys.

Other Animal Pharmacology:
No cardiovascular effects occurred in dogs given a single oral dose of 100 mg/kg and in an extracorporeal shunt test in rabbits, danazol at 400 mg/kg/day for 14 days had no effect on either thrombus weight or bleeding time while β-estradiol caused a 96% increase in thrombus weights and a significant lowering of bleeding time. Danazol had no central nervous system effects in mice given single oral doses up to 300 mg/kg.

Disposition in Animals:
The metabolic fate of danazol has been studied in the rat and monkey using radiolabelled compound. (Davison et al. 1976). The drug was extensively metabolized; about 60 urinary end products were noted by thin layer chromatographic techniques. Only small quantities of unchanged danazol were found in the excreta of the laboratory animals. The major metabolite of danazol is 2-hydroxymethylethisterone. Lesser quantities of Δ^1-2-hydroxymethylethisterone and ethisterone were isolated and identified. Trace quantities of 3 other metabolites were identified; 2-ketoethisterone, 6β-hydroxy-2-hydroxy-methylethisterone and Δ^{1-}6β-hydroxy-2-hydroxymethylethisterone. The combined metabolites accounted for about 11% of the radioactivity of the dose.

In the rat, the major portion of the radioactivity was excreted in the fecal material, while in the monkey about equal portions were eliminated in the urine and feces. Fecal radioactivity does not represent unabsorbed drug, but results from biliary excretion. In the rat, about 70% of the administered radioactivity was recovered in the bile within 12 hours. In the monkey, an average of 40% of administered radioactivity was found in the bile after 8.5 hours; urine collected over the same time period contained 24% of the radioactivity of the dose.

Clinical Pharmacology:
Laboratory studies related to drug efficacy were carried out to evaluate the capacity of danazol to alter other hormone parameters possibly influenced by changes in the pituitary-gonadal system. Results of serial measurements of serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) showed a complete blockage of the mid-cycle ovulatory surge at doses of 200 to 800 mg daily (Greenblatt et al. 1971, Guillebaud et al. 1977). Measurements of serum estrogen and progesterone showed these steroids to be held to low basal levels during danazol administration (Wood et al. 1975, Chimbira et al. 1980). In the male, there was a decrease in plasma androgens (Sherins et al. 1971). In two studies in which adrenal function was measured, danazol had no adverse effects (Franchimont and Cramilion 1977, Wentz et al. 1975).

In an earlier study in normal males, after three weeks of 200 mg/day danazol treatment, basal plasma cortisol and the responses of cortisol and dehydroepiandrosterone (D) levels to ACTH were normal but basal D levels were lower after the three-week treatment than the pre-treatment values (Sherins et al. 1971).

In vivo, danazol is extensively metabolized (Davison et al. 1976). One study involving 24 healthy female adult subjects receiving a 200 mg oral dose of danazol was used to determine the pharmacokinetic parameters. The mean plasma concentration data was computer-fitted to a one-compartment open body model. The concentration of danazol in the plasma is given by the equation:

$$C=Ae^{-K_e (T-T_0)}-e^{-K_a(T-T_0)}$$

where A is the constant 61.69 ng/ml K_e is the apparent first-order elimination constant 0.024 hr^{-1}, K_a is the first-order absorption rate constant 2.199 hr^{-1},T is the time after medication T_0 the lag time (0.698 hr) before the absorption process begins. The apparent first-order elimination half-life for danazol was 29 hr. The mean maximum plasma concentration was about 60 ng/mL after a single 200 mg dose of danazol. At steady-state conditions, following a dosage regimen of 200 mg per day in two equally divided doses, the mean maximum plasma concentration of danazol was about three times as high 183 ng/ml (Potts et al. 1980).

The bioequivalence of formulations of the 50 mg, 100 mg and 200 mg capsules has been demonstrated (Lloyd-Jones et al. 1977, Peterson et al. 1978). The time required to attain steady-state plasma concentrations of danazol depends on the administered dose. With doses of 100 mg of danazol twice daily, steady-state was reached in 7 days; however, when 200 mg of danazol b.i.d. is given, at least 14 days are required for plasma levels to reach the steady-state (Davison et al. 1975, Williams, et al. 1978).

TOXICOLOGY

Acute Toxicity:
The acute toxicity of danazol in several animal species has been shown to be extremely low:

SPECIES	ROUTE	LD_{50}
Mouse	oral	> 16,000 mg/kg
Mouse	s.c.	> 8,000 mg/kg s.c.
Rat	oral	> 16,000 mg/kg
Rabbit	oral	> 5,000 mg/kg
Dog	oral	> 5,000 mg/kg

Subacute and Chronic Toxicity:
When male and female albino rats were given single daily oral doses of 5, 25, 125 or 625 mg/kg danazol for one year, no overt pharmacologic effects or deaths related to the effects of medication occurred in any group. Danazol was well tolerated when given to rhesus monkeys in daily oral doses of 5, 20 or 80 mg/kg for 53 weeks and daily oral doses of 320 to 1280 mg/kg for 7 weeks were also well tolerated. Danazol was administered orally to male and female albino rats and rhesus monkeys at doses of 20, 100, or 500 mg/kg in the capsule formulation daily for 22-1/2 and 24 months, respectively.

No significant toxicological findings were observed in the rats with regard to behavioral changes, ocular examination, blood pressure, food consumption, growth and survival rates, hematology, blood and urine biochemical parameters, incidence and type of neoplasms and histochemistry. Atrophic changes in the male sex organs were observed in all groups in the study, including the GT control and placebo groups but their incidence was higher in the 500 mg/kg group than in any other group, suggesting a drug-related effect which was probably due to the basic pituitary gonadotrophin inhibitory activity of the drug. Dose-related increases in liver weights, most prominent in males were also observed. However, microscopic studies failed to indicate specific target organ changes which could be specifically and exclusively ascribed to the drug.

No significant toxicological findings were observed in the monkeys with respect to growth rate, food consumption, ophthalmoscopic examination, osseous changes, respiratory rate, blood pressure, body temperature, hematology, urine analysis, ECG studies and blood clotting mechanism. Of the many standard blood biochemical parameters studied, only five appeared to be affected by medication with danazol: total protein and albumin were slightly depressed, alkaline phosphatase slightly to markedly depressed, total cholesterol was slightly to moderately depressed, and SGPT was slightly to moderately elevated in the 100 and 500 mg/kg groups. Measurement of thyroid function revealed normal free T_4levels and slight dose-related elevations in T_3,T_4 and PBI levels. However, none of the elevations were in the thyrotoxic range and microscopic study of the thyroids did not reveal any drug-related effects. Tissue changes, related to the pituitary inhibiting properties of danazol were observed in the mammary glands and sex organs. Such changes were either absent or minimal at 20 mg/kg. Increased adrenal and pituitary

weights were seen in males but not in females. In the liver a dose-related increase in weight, prominent bile ducts and hypertrophy of centrolobular cells in the 100.0 and 500.0 mg/kg groups were observed.

No gross or microscopic evidence of any neoplastic changes were found.

Reproduction Studies:
Six toxicological studies have been carried out to evaluate the potential effects of danazol on the reproductive process and the development of the fetus.

These included:

Teratology: Oral administration to pregnant albino rats.
Oral administration to pregnant New Zealand white rabbits.
Oral administration to pregnant rhesus monkeys.

Perinatal: Postnatal study in albino rats.
Fertility and reproductive performance of albino rats (2 studies).

In the 3 species used danazol was not teratogenic. No consistent syndrome of anatomic alterations was found which could be defined as teratogenic. Of particular significance was the lack of any teratogenic effect in the rhesus monkey. In this primate experiment, thalidomide used as a positive control, was both teratogenic and embryotoxic.

Preliminary results in juvenile monkeys (Macacca mulatta), treated with danazol for one year and subsequently observed over a period of several years, indicate that danazol has no long-term effect on the reproductive function of female animals. However, impairment of reproductive performance of male animals cannot be excluded based on this study.

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PART III: CONSUMER INFORMATION

Pr CYCLOMEN®
(danazol capsules, USP)

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CYCLOMEN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- treatment of endometriosis
- relief of severe pain and tenderness associated with fibrocystic breast disease

What it does:

The lining of the uterus is called the endometrium. Part of it is shed during your menstrual period (period). In endometriosis, endometrium-like tissue is found outside the uterus, such as around the uterus, ovaries, intestines and other organs in the pelvis. As with normal endometrial tissue, this tissue can be shed during your period. Some women with endometriosis have symptoms such as painful periods, pelvic pain, pain during intercourse and painful bowel movements.

When used to treat endometriosis, CYCLOMEN changes the endometrium so that it becomes inactive and shrinks in size. Relief from painful symptoms usually begins a few weeks after starting CYCLOMEN.

When used to treat benign fibrocystic breast disease, CYCLOMEN relieves pain and tenderness in the breast and may also cause nodules in the breast to shrink. Pain and tenderness should begin to disappear after about 1 month. Nodules do not start to shrink in size until after 2 - 3 months of treatment.

After starting with CYCLOMEN you will probably have one more period. Your periods will then stop while you are taking CYCLOMEN, however, you may have occasional spotting or vaginal bleeding. After you stop taking CYCLOMEN your periods will start again, usually within 2 - 3 months.

When it should not be used:

CYCLOMEN should not be used if you:
- have abnormal vaginal bleeding, not diagnosed by your doctor
- have genital or breast tumors
- have liver, kidney or heart problems
- are pregnant
- are breastfeeding
- have porphyria
- have an androgen (male sex hormone) - dependent tumor
- have a tendency to form blood clots, or problems (past or current) with blood clots forming in your blood vessels
- have a known allergy to CYCLOMEN or any of its nonmedicinal ingredients (see below)
- are taking a medicine called simvastatin (used to treat high cholesterol).

What the medicinal ingredient is: Danazol

What the nonmedicinal ingredients are: Maize starch, red iron oxide (50 mg and 200 mg capsules), black iron oxide (100 mg capsules), yellow iron oxide (200 mg capsules), gelatin, lactose monohydrate, magnesium stearate, talc, titanium dioxide.

What dosage forms it comes in:
Capsules : 50 mg, 100 mg, 200 mg

WARNINGS AND PRECAUTIONS

- CYCLOMEN can cause harm to an unborn baby when given to pregnant women
- Use of CYCLOMEN to treat endometriosis may increase the risk of cancer of the ovaries or may induce tumors of the liver.

BEFORE you use CYCLOMEN talk to your doctor or pharmacist if you have:
- liver, kidney or heart disease
- high blood pressure
- atherosclerosis (hardening of the arteries)
- diabetes
- epilepsy
- blood clots

- suffer from migraines
- had an organ transplant
- recently undergone surgery

Talk to your doctor if you are experiencing any of the following symptoms with CYCLOMEN:

- development of male characteristics (virilization) such as deepening of the voice, growth of body hair, clitoral thickening. In rare cases, these effects may not be reversible.
- headache or changes in vision due to an increase fluid pressure within the skull.
- yellowing of the skin or eye (jaundice), loss of appetite, nausea, vomiting, fever, feeling unwell, unusual tiredness, itching, unusual darkening of the urine, right upper stomach area pain or discomfort. CYCLOMEN may cause liver problems, including life-threatening liver failure.
- a blood clot in the leg (pain and swelling of the calf), or in the lung (sharp pain in the chest, coughing blood, or sudden shortness of breath)

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with CYCLOMEN include:

- coumadin (warfarin)-type anticoagulants (used to prevent blood clots from forming)
- carbamazepine, phenytoin and phenobarbital (drugs used to treat epilepsy)
- cyclosporin and tacrolimus (used to reduce organ rejection after an organ transplant operation)
- insulin or oral hypoglycemic agents (used to treat diabetes)
- anti-hypertensive drugs (used to treat high blood pressure)
- statin drugs (used to lower blood cholesterol such as simvastatin, atorvastatin and lovastatin). The concomitant administration of CYCLOMEN with simvastatin is contraindicated.

PROPER USE OF THIS MEDICATION

Usual Dose:

Treatment with CYCLOMEN should be uninterrupted, with no missed doses to be effective. CYCLOMEN should be started during your period. It is important that you use a non-hormonal method of contraception (such as diaphragm with contraceptive jelly, IUD, condoms) while taking CYCLOMEN.

Endometriosis: The usual total dose is 200 to 800 mg a day. This is given in 2 - 4 divided doses a day for 3 to 6 months. For severe cases, the starting dose is 800 mg a day. The maximum recommended dose is 800 mg a day.

Fibrocystic Breast Disease: The usual total dose is 100 - 400 mg a day. This is given in 2 doses a day for 6 months.

After stopping CYCLOMEN, if your symptoms return, talk to your doctor, you may be able to start treatment again.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department, or regional Poison Control Center immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of CYCLOMEN, you should take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

CYCLOMEN causes changes to your body's normal sex hormone levels, as a result, you may notice the following side effects: acne, edema (swelling, especially of the hands, feet, and face), mild growth of body hair, decrease in breast size, deepening of the voice, oiliness of the skin or hair, weight gain, increase in size of the clitoris, flushing, sweating, vaginal itching and dryness, vaginal burning, vaginal spotting or bleeding, nervousness, mood changes, visual hallucinations or disturbances, and seizures.

Other rare side effects are: jaundice (yellowing of the skin), liver tumors, liver and pancreatic disorders, rashes.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharma-cist**
	Only if severe	**In all cases**	
Rare			
Nervous system disorders: Persistent headache		✓	
Gastrointestinal disorders: Pancreatic disorders (persistent abdominal pain)		✓	
Very Rare			
Pulmonary disorders: Pneumonia	✓		
Skin and subcutaneous tissue disorders: Severe skin rash	✓		
Blood and lymphatic disorders: Persistent abdominal pain		✓	
Unknown frequency			
Liver injury with symptoms such as: loss of appetite, nausea, vomiting, fever, feeling unwell, unusual tiredness, itching, yellowing of the skin or the whites of the eyes (jaundice), unusual darkening of the urine, right upper stomach area pain or discomfort.		✓	

This is not a complete list of side effects. For any unexpected effects while taking CYCLOMEN, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at: www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

CYCLOMEN should be stored in a safe place at room temperature (15-30^0 C).

Keep out of the reach of children.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at: www.sanofi.ca or by contacting the sponsor, sanofi-aventis Canada Inc., at: 1-800-265-7927

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