MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3 Product Information

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product:

Danazol Capsules USP 200 mg (NAZOL CAPSULES)

1.1 (Invented) name of the medicinal product:

Generic Name/INN Name:

Danazol Capsules USP 200 mg

1.2 Strength:

Each hard gelatin capsule contains

Danazol USP….200 mg

Excipients……q.s.

Note: Approve colors used in empty hard gelatin capsule shell

1.3 Pharmaceutical form:

Solid Dosage Form-Capsules

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2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Spec.	Label Claim (mg)	Std. Qty./Cap (mg)	% w/w	Function
Direct Mixing.						
1.	Danazol *	USP	200.000	200.000	43.48	Active Pharmaceutical Ingredient
2.	Maize Starch **	BP	--	70.000	15.22	Diluent/Binder
3.	Lactose Monohydrate	BP	--	110.000	23.91	Diluent
4.	Sodium Lauryl Sulfate	BP	--	12.000	2.61	Surfactant
Binding.						
5.	Purified water***	BP	--	60.000	---	Granulating vehicle
Lubrication.						
6.	Magnesium Stearate	BP	--	8.000	1.74	Lubricant
7.	Maize Starch	BP	--	55.000	11.96	Disintegrant
8.	Purified Talc	BP	--	5.000	1.09	Lubricant
Average net content of capsule				**460.000**	--	--
9.	EHG caps '0' Green/Green.	In-house	--	1 Capsule = 95 mg	--	Capsule Shell
Average weight of filled capsule				**555.000**	**100.00%**	--

NOTE:

* The quantity of Danazol has to be calculated as per Assay and LoD.

**Quantity of Maize Starch will vary as per the quantity of the API.

*** The materials that will not remain in the final product.

3. Pharmaceutical form:

Dosage Form: Solid Dosage Form-Capsules

Visual & Physical characteristics of the product:

A green/green coloured hard gelatin capsules size "0" containing pale yellow coloured granular powder.

4. Clinical particulars

4.1. Therapeutic indications:

Danazol capsules are recommended for the treatment of:

- Endometriosis. To control pain, pelvic tenderness and other associated symptoms and to resolve or reduce the extent of endometriotic foci. Danazol capsules may be used as sole therapy, in preparation for or following surgery or in patients not responding to other treatments.

- Dysfunctional uterine bleeding presenting as menorrhagia. To control excessive blood loss and to control associated dysmenorrhoea.
- For the treatment of severe cyclical mastalgia with or without nodularity (fibrocystic disease) unresponsive to counselling or simple analgesics. To reduce pain, tenderness and nodularity.
- For the control of benign, multiple or recurrent breast cysts in conjunction with aspiration.
- Severe symptomatic gynaecomastia, both idiopathic as well as drug induced, to reduce the size of the breast and to control associated pain and tenderness.
- Pre-operative thinning of the endometrium prior to hysteroscopic endometrial ablation.

4.2. Posology and method of administration:

Adults

The usual range of dosage is 200 mg to 800 mg daily in up to four divided doses.

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. In fertile females, Danazol should be started during menstruation, preferably on the first day, to avoid exposing a pregnancy to its possible effects. Where doubt exists, appropriate checks should be made to exclude pregnancy before starting medication. Females of child-bearing age should employ non-hormonal contraception throughout the course of treatment.

In endometriosis, the recommended dosage is 200-800 mg daily in a course of treatment lasting normally three to six months, although up to nine months may be necessary in some cases. Dosage should be increased if normal cyclical bleeding still persists after two months therapy, a higher dosage (not exceeding 800 mg per day) may also be needed for severe disease.

For dysfunctional uterine bleeding presenting as menorrhagia, the dosage should be 200 mg daily, normally for 3 months.

In severe cyclical mastalgia, treatment should commence at a dose of 200-300 mg daily, according to the severity of the symptoms, a course of treatment normally lasting 3-6 months.

In benign breast fibrocystic disease, treatment should commence at a dose of 300 mg daily, a course of treatment normally lasting 3 to 6 months.

In gynaecomastia a six-month course of therapy is recommended at a dose of 200 mg daily in adolescents which may be increased to 400 mg daily if no response is obtained after two months. Adults may be given 400 mg daily.

For pre-operative thinning of the endometrium, the usual dose is 400-800 mg daily given as a continuous course normally lasting 3-6 weeks.

Elderly

Danazol Capsules are not recommended.

Pediatric population

Danazol Capsules are not recommended.

Method of administration:

For oral administration only.

4.3. Contraindications:

- Pregnancy
- Breastfeeding: danazol may be excreted in breast milk
- Markedly impaired hepatic, renal or cardiac function
- Porphyria: danazol can induce ALA synthetase activity and hence porphyrin metabolism
- Active thrombosis or thromboembolic disease and a history of such events
- Androgen dependent tumor
- Abnormal genital bleeding that has not been fully investigated.
- Hypersensitivity Concomitant administration with simvastatin

4.4. Special warnings and precautions for use:

In view of its pharmacology, known interactions and side effects, particular care should be observed when using danazol in patients with hepatic or renal disease, hypertension or other cardiovascular disease and in any state, which may be exacerbated by fluid retention as well as in diabetes mellitus, polycythaemia, epilepsy, lipoprotein disorder, in those with a history of thrombosis, and in those who have shown marked or persistent androgenic reaction to previous gonadal steroid therapy. Adjustment in concomitant therapy may be called for particularly in patients with hypertension, diabetes mellitus or epilepsy when introducing or discontinuing danazol as well as during Danazol treatment. Caution is advised in patients with migraine.

Until more is known, caution is advised in the use of danazol in the presence of known or suspected malignant disease (see also contraindications). Before treatment initiation, the presence of hormone-dependent carcinoma should be excluded at least by careful clinical examination, as well as if breast nodules persist or enlarge during danazol treatment. In the event of virilization, Danazol should be

withdrawn. Whilst androgenic reactions will generally prove reversible, continued use of danazol in the face of evident virilization is likely to cause irreversible androgenic effects.

Danazol should be stopped if any clinically significant adverse event arises, and particularly if there is evidence of papilloedema, headache, visual disturbances or other signs or symptoms of raised intracranial pressure, jaundice or other indication of significant hepatic disturbance, thrombosis or thromboembolism.

Danazol should be initiated during menstruation. An effective, non-hormonal method of contraception should be employed. The lowest effective dose of danazol should always be sought.

Experience of long-term therapy with danazol is limited. Whilst 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. The long-term risk of 17-alkylated steroids (including benign hepatic adenomata, hepatocellular focal nodular hyperplasia, peliosis hepatis and hepatic carcinoma), should be considered when danazol, which is chemically related to these compounds, is used for periods longer than those normally recommended. 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 - patients treated for endometriosis. Danazol capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction:

Anti-Convulsant Therapy*:* danazol may affect the plasma level of carbamazepine and, possibly the patient's response to this agent and to phenytoin. With phenobarbital it is likely that similar interaction would occur.

Anti-Diabetic Therapy*:* danazol can cause insulin resistance.

Oral Anti-Coagulant Therapy*:* danazol can potentiate the action of warfarin.

Anti-Hypertensive Therapy*:* Possibly through promotion of fluid retention, danazol can oppose the action of anti-hypertensive agents.

Ciclosporin and tacrolimus*:* danazol can increase the plasma level of ciclosporin and tacrolimus, leading to an increase of the renal toxicity of these drugs.

Concomitant Steroids*:* Although specific instances have not been described, it is likely that interactions will occur between danazol and gonadal steroid therapy.

Migraine Therapy*:* danazol may itself provoke migraine and possibly reduce the effectiveness of medication to prevent that condition.

Ethyl Alcoho*l:* Subjective intolerance in the form of nausea and shortness of breath has been reported.

Alpha Calcidol*:* danazol may increase the calcaemic response in primary hypoparathyroidism necessitating a reduction in dosage of this agent.

Interactions with laboratory function tests: danazol treatment may interfere with laboratory determination of testosterone or plasma proteins.

Statins*:* The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with statins metabolised by CYP3A 4 such as simvastatin, atorvastatin and lovastatin.

4.6. Pregnancy and lactation:

Pregnancy

There is epidemiological and toxicological evidence of hazard in human pregnancy. Danazol is known to be associated with the risk of virilization to the female foetus if administered during human pregnancy. Danazol should not be used during pregnancy. Women of childbearing age should be advised to use an effective, non-hormonal, method of contraception. If the patient conceives during therapy, Danazol should be stopped.

Breast-feeding

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

4.7. Effects on ability to drive and use machines:

Danazol has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects:

The possible causal relationship between danazol and many of the following events reportedly associated with its use remains to be defined.

Blood and lymphatic system disorders

Increase in red cell and platelet count. Reversible erythrocytosis or polycythaemia may be provoked. Eosinophilia, leucopenia, splenic peliosis and thrombocytopenia have also been noted.

Endocrine disorders

Androgenic effects:

Acne, weight gain, increased appetite, seborrhoea, hirsutism, hair loss, voice change, which may take the form of hoarseness, sore throat or of instability or deepening of pitch. Hypertrophy of the clitoris, fluid retention.

Other endocrine effects:

Menstrual disturbances in the form of spotting, alteration of the timing of the cycle and amenorrhoea. Flushing, vaginal dryness, vaginal irritation and reduction in breast size. Vaginal dryness and irritation and reduction in breast size may reflect a lowering of oestrogens.

Although cyclical bleeding and ovulation usually return within 60-90 days after danazol, persistent amenorrhoea has occasionally been reported. Modest reduction in spermatogenesis.

Metabolism and nutrition disorders

Insulin resistance may be increased in diabetes mellitus but symptomatic hypoglycaemia in non-diabetic patients has also been reported as an increase in plasma glucagon level, mild impairment of glucose tolerance.

A temporary alteration of lipoproteins in the form of an increase in LDL cholesterol, a decrease in HDL cholesterol, affecting all subfractions, and a decrease in apolipoproteins A1 and AII. The clinical significance of these changes is not established.

Induction of aminolevulinic acid (ALA) synthetase, and reduction in thyroid binding globulin, T4, with increased uptake of T3 but without disturbance of thyroid stimulating hormone or free thyroxin index, is also likely during therapy.

Psychiatric disorders

Emotional lability, anxiety, depressed mood, nervousness and changes in libido.

Nervous system disorders

Dizziness, headache, vertigo, benign intracranial hypertension.

Danazol may aggravate epilepsy and expose the condition in those so predisposed.

Fluid retention may explain the occasional reports of carpal tunnel syndrome. Danazol may also provoke migraine.

Eye disorders

Visual disturbances which may take the form of blurring or difficulty in focusing and in wearing contact lenses or need for temporary alteration in refractive correction have been noted.

Cardiac disorders

Hypertension, palpitation and tachycardia.

Thrombotic events including sagittal sinus, cerebrovascular thrombosis as well as arterial thrombosis. Myocardial infarction.

Vascular disorders

Flushing, exacerbation of hypertension

Respiratory, thoracic and mediastinal disorders

Pleuritic pain, interstitial pneumonitis

Gastrointestinal disorders

Nausea, epigastric pain

Hepatobiliary disorders

Modest increase in serum transaminase levels and rarely cholestatic jaundice, benign hepatic adenomata and pancreatitis. Peliosis hepatis as well as malignant hepatic tumour have been observed with long term use.

Hepatocellular injury, hepatic failure, jaundice hepatocellular, hepatocellular focal nodular hyperplasia.

Skin and subcutaneous tissue disorders

Rashes, which may be maculopapular, petechial, or purpuric or may take an urticarial form and may be accompanied by facial oedema. Associated fever has also been reported. Rarely, sun-sensitive rash has been noted. Inflammatory erythematous nodules, changes in skin pigmentation, exfoliative dermatitis and erythema multiforme have also been reported.

Musculoskeletal and connective tissue disorders

Backache and muscle cramps which can be severe. Creatine phosphokinase levels may also rise. Muscle tremors, fasciculation, limb pain, joint pain and joint swelling have also been reported.

Renal and urinary disorders

Haematuria has rarely been reported with prolonged use in patients with hereditary angioedema.

General disorders and administration site conditions

Fatigue

4.9. Overdose:

Available evidence suggests that acute overdosage would be unlikely to give rise to immediate serious reaction.

In the case of acute overdosage consideration should be given to reducing the absorption of the drug with activated charcoal, and the patient should be kept under observation in case of any delayed reactions.

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5. Pharmacological properties:

Pharmacotherapeutic group: sex hormones and modulators of the genital system.

ATC Code: G03XA01

5.1. Pharmacodynamic properties:

Danazol, 17a-pregna-2,4-dien-20-yno(2,3-d)-isoxazol-17-ol, is a synthetic steroid derived from ethisterone. Its pharmacological properties include:

1. Relatively marked affinity for androgen receptors, less marked affinity for progesterone receptors and least affinity for oestrogens receptors. Danazol is a weak androgen but in addition antiandrogenic, progestogenic, anti-progestogenic, oestrogenic and antioestrogenic actions have been observed.

2. Interference with the synthesis of gonadal steroids, possibly by inhibition of the enzymes of steroidogenesis, including 3β hydroxysteroid dehydrogenase,17β hydroxysteroid dehydrogenase, 17 hydroxylase, 17, 20 lyase, 11β hydroxylase, 21 hydroxylase and cholesterol side chain cleavage enzymes, or alternatively by inhibition of the cyclic AMP accumulation usually induced by gonadotrophic hormones in granulosa and luteal cells.

3. Inhibition of the mid-cycle surge of FSH and LH as well as alterations in the pulsatility of LH. Danazol can also reduce the mean plasma levels of these gonadotrophins after the menopause.

4. A wide range of actions on plasma proteins, including increasing prothrombin, plasminogen, antithrombin III, alpha-2 macroglobulin, C1 esterase inhibitor, and erythropoietin and reducing fibrinogen, thyroid binding and sex hormone binding globulins. Danazol increases the proportion and concentration of testosterone carried unbound in plasma. The suppressive effects of danazol on the hypothalmic-pituitary-gonadal axis are reversible, cyclical activity reappearing normally within 60-90 days after therapy. Danazol appears to exert its principal pharmacological activity in the endocrine system as an inhibitor of gonadotrophin synthesis and/or release by the pituitary. The mechanisms by which danazol exerts its therapeutic effect are incompletely understood and there are considered to be four possible mechanisms of the action as follows:

- Direct inhibition of gonadotrophin-releasing hormone secretion and/or gonadotrophin secretion.
- Direct inhibition of multiple enzymes of steroidogenesis.
- Interaction with intracellular enzymes of steroidogenesis.
- Alteration of endogenous steroid metabolism.

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5.2. Pharmacokinetic properties:

Absorption: Danazol is absorbed from the gastrointestinal tract, peak plasma concentrations of 50-80ng/ml being reached approximately 2-3 hours after dosing. Compared to the fasting state, the bioavailability has been shown to increase 3-fold when the drug is taken with a meal with a high fat content. It is thought that food stimulates bile flow which facilitates the dissolution and absorption of danazol, a highly lipophilic compound.

A dose of danazol 100 mg twice daily gives a steady state plasma level in 7 days but a dose of 200 mg twice daily does not give a steady state plasma level unit 14 days.

The apparent plasma elimination half-life of danazol in a single dose is approximately 3-6 hours. With multiple doses this may increase to approximately 26 hours.

Biotransformation: In humans, 2-hydroxymethylethisterone and ethisterone are the major urinary metabolites with unchanged danazol absent. The antigonadotrophic activity of danazol appears to be exerted by the unchanged compound and not by one of its metabolites, for the major metabolites are devoid of antigonadotrophic action. The activity of danazol is slightly

increased when it is administered with substances which inhibit the action of drug metabolising enzymes.

None of the metabolites of danazol, which have been isolated, exhibits pituitary inhibiting activity comparable to that of danazol.

Elimination: Few data on excretion routes and rates exist. In the monkey 36% of a radioactive dose was recoverable in the urine and 48% in the faeces within 96 hours.

5.3 Preclinical safety data

None

6. Pharmaceutical particulars:

6.1. List of Excipients:

Maize Starch, Lactose Monohydrate, Sodium Lauryl Sulphate, Magnesium Stearate, Purified Talc.

6.2. Incompatibilities:

The absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf life:

36 months

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6.4. Special precautions for storage:

Store at a temperature not exceeding 30 ºC.

6.5. Nature and contents of container:

Primary Pack: 10 capsules packed in one ALU-PVC blister.

Secondary Pack: Such 3 ALU-PVC blisters are packed in monocarton with package insert.

6.6. Special precautions for disposal:

No special requirements.

7. Applicant:

Chez Resources Pharmaceutical Limited

No. 7, Calabar Street, Fegge, Onitsha,

Anambra State, NIGERIA

Name and Address of manufacturer:

M/s. Bharat Parenterals Limited

Survey No. 144 - A, Jarod Samlaya Road,

Village: Haripura, Tal. Savli,

Dist.- Vadodara – 391520, Gujarat, India.

Tel. +91-99250 25635