ANARGIL

1. NAME OF THE MEDICINAL PRODUCT

Anargil 100mg capsules, hard
Anargil 200mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100mg or 200mg danazol.

Excipient with known effect: lactose.
Each 100mg capsule contains 123mg of lactose.
Each 200mg capsule contains 35mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.
Anargil 100mg capsules hard: yellow-yellow hard gelatine capsules, size 2
Anargil 200mg capsules hard: orange-orange hard gelatine capsules, size 2, printed "Medochemie"
For oral administration.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Danazol is recommended for the treatment of endometriosis and associated infertility, benign breast disease (e.g. fibrocystic mastitis) and menorrhagia.

Danazol has also been used to treat virginal breast hypertrophy, primary constitutional precocious puberty, gynaecomastia and other similar endocrine disorders where regulation of the release of pituitary gonadotrophins LH and FSH would be of therapeutic value.

Danazol has also been used in prophylaxis of hereditary angioedema.

4.2. Posology and method of administration

It is used in the treatment of endometriosis. The usual initial dose is 400mg daily in 2 to 4 divided doses, starting on the first day of the menstrual cycle (to exclude pregnancy); daily doses of 800mg are also employed.

Danazol is also used in the treatment of benign breast disorders including gynaecomastia, fibrocystic breast disease and pubertal breast hypertrophy in usual divided doses of 100mg to 400mg daily.

In primary constitutional precocious puberty 100 to 400mg daily may be given according to the child's age and weight.

In the prophylaxis of hereditary angioedema, the usual dose is 400 mg daily. Reduce to 200 mg daily after 2 months attack free period.

Method of administration
Capsules are for oral administration.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy
- Breast feeding
- Markedly impaired hepatic, renal or cardiac function
- Porphyria
- Active thrombosis or thromboembolic disease and a history of such events
- Androgen dependent tumour
- Undiagnosed abnormal genital bleeding
- Concomitant administration with simvastatin (see section 4.5)

4.4. Special warnings and precautions for use

Special warnings

In the event of virilisation, danazol should be withdrawn. Androgenic reactions generally prove reversible, but continued use of Anargil after evidence of androgenic virilisation increases the risk of irreversible androgenic effects.

Anargil 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.

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, peliosis hepatis and hepatic carcinoma), should be considered when danazol, which is chemically related to those compounds, is used.

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.

Precautions

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, and in those who have shown marked or persistent androgenic reaction to previous gonadal steroid therapy.

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 section 4.3). 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 addition to clinical monitoring in all patients, appropriate laboratory monitoring should be considered which may include periodic measurement of hepatic function and haematological state. For long-term treatment (> 6 months) or repeated courses of treatment, biannual hepatic ultrasonography is recommended.

Danazol should be initiated during menstruation. An effective, non -hormonal method of contraception should be employed (see section 4.2 and 4.6).

The lowest effective dose of Anargil should always be sought.

Anargil contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interactions 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 alcohol: 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 (see also section 4.8)
- 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. Fertility, 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 virilisation 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 breast-feeding 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
Blood and lymphatic system disorders
Not known: Increase in red cell and platelet count. Reversible polycythaemia, leucopoenia, thrombocytopenia, eosinophilia and splenic peliosis.

Endocrine disorders
Not known:
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, changes in libido, vaginal irritation and reduction in breast size.
Modest reduction in spermatogenesis.

Metabolism and nutrition disorders
Not known: Increased insulin resistance, increase in plasma glucagon, mild impairment of glucose tolerance.
Increase in LDL cholesterol, decrease in HDL cholesterol, affecting all subfractions, and decrease in apolipoproteins AI and AII.
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 levothyroxine index.

Psychiatric disorders
Not known: Emotional lability, anxiety, depressed mood and nervousness.

Nervous system disorders
Not known: Dizziness, headache, vertigo, benign intracranial hypertension, migraine.
Aggravation of epilepsy, carpal tunnel syndrome.

Eye disorders
Not known: Visual disturbances such as blurring of vision, difficulty in focusing, difficulty in wearing contact lenses and refraction disorders requiring correction.

Respiratory, thoracic and mediastinal disorders
Not known: Pleuritic pain, interstitial pneumonitis.

Gastrointestinal disorders
Not known: Nausea, epigastric pain.

Cardiac disorders
Not known: Hypertension, palpitations and tachycardia.
Thrombotic events including sagittal sinus, cerebrovascular thrombosis as well as arterial thrombosis. Myocardial infarction.

Hepatobiliary disorders
Not known: Isolated increases in serum transaminase levels, cholestatic jaundice, benign hepatic adenomata and pancreatitis. Peliosis hepatitis as well as malignant hepatic tumour observed with long term use.
Hepatocellular injury, hepatic failure, jaundice hepatocellular, hepatocellular focal nodular hyperplasia.

Skin and subcutaneous tissue disorders
Not known: Rashes, which may be maculopapular, petechial or purpuric and may be accompanied by fever or may take an urticarial form and may be accompanied by facial oedema. Sun-sensitive rash.
Inflammatory erythematosus nodules, changes in skin pigmentation, exfoliative dermatitis and erythema multiforme.

Musculoskeletal and connective tissue disorders
Not known: Backache and muscle cramps which can be severe, with elevation of creatine phosphokinase levels. Muscle tremors, fasciculation, limb pain, joint pain and joint swelling.

Renal and urinary disorders
Not known: Haematuria with prolonged use in patients with hereditary angioedema.

General disorders and administration site conditions
Not known: Fatigue.

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

Management
In the case of acute overdose 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.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Pharmacotherapeutic group: sex hormones and modulators of the genital system, antigonadotropins and similar agents, ATC code: G03XA01

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

5.2. Pharmacokinetic properties
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.
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.
None of the metabolites of danazol, which have been isolated, exhibits pituitary inhibiting activity comparable to that of danazol.
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
There are no preclinical data of relevance to the prescriber, which are additional to those already included in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Anargil capsules contain maize starch, povidone, lactose, croscarmellose sodium, sodium lauryl sulphate and magnesium stearate.
Anargil 100mg capsules' shell contain gelatin, quinolone yellow (E104), iron oxide yellow (E172) titanium dioxide (E171) and sodium lauryl sulphate
Anargil 200mg capsules' shell contain gelatin, Erythrosin (E127), quinolone yellow (E104) and titanium dioxide (E171).

6.2. Incompatibilities

None.

6.3. Shelf life

5 years

6.4. Special precautions for storage

Store below 30^{o}C in the original package, in order to protect from light and moisture.

6.5. Nature and contents of container

Polyvinylchloride-aluminium blisters of ten capsules. Ten such blisters (**100 capsules**) are contained in a card carton.

6.6. Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6. MANUFACTURER

MEDOCHEMIE LTD. (Central Factory), 1-10 Constantinoupoleos Street, 3011 Limassol, Cyprus

7. PRODUCT REGISTRATION HOLDER

KOMEDIC SDN BHD., No. 4 Jalan PJS 11/14, Bandar Sunway, 46150 Petaling Jaya, Selangor, MALAYSIA

8. PRODUCT REGISTRATION NUMBERS

Anargil 100mg capsules: MAL19890682AZ
Anargil 200mg capsules: MAL19871961AZ

9. DATE OF REVISION OF THE TEXT

March 2023