DANATROL

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Danatrol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Danatrol contains as active substance 100 resp. 200 mg of danazol per capsule.

3. PHARMACEUTICAL FORM

Capsule

4. CLINICAL PARTICULARS

4.1 Therapeutical indications:

- Symptomatic treatment of endometriosis
- Benign fibrocystic breast disease such as multiple or recurring breastcysts (mastopathia chronica systica): symptomatic relief of severe pain and tenderness.
- Profylactic treatment of hereditary angioneurotic edema attacks based on functional C1 esterase inhibitor deficiency

For the first two indications: Danazol should be used only in patients not responsive to other therapeutic measures or for whom such measures are inadvisable.

4.2 Posology and method of administration:

For maintenance therapy the lowest dosage that is still effective should be used.

Danazol is for oral administration only.

Danazol treatment should be started during menstruation. An effective, non-hormonal contraceptive method should be used and pregnancy should be ruled out beforehand (see section 4.6 “pregnancy and lactation”).

Symptomatic treatment of endometriosis
To reach amenorrhea a starting dosage of 600-800 mg/day of Danatrol can be given during the first month, starting on the first day of the cycle. Following a favourable response, the dosage may be reduced.
Usually this will be the case after 30-90 days; a maintenance dosage of 400-600 mg will as a rule be sufficient. These dosages can be taken as 2 or 3 doses divided over the day.

Benign fibrocystic breast disorders
In case of very serious symptoms they can be treated with 400 mg/day during 4-6 months. In less serious cases 200-100 mg/day is recommended during a shorter period of treatment.
It is however recommended to continue the treatment for at least 1-2 months, after disappearance of the subjective symptoms. A treatment of 3-6 months will be sufficient in most cases. The maximum duration of treatment is 6-9 months.

Heriditary angioneurotic edema
The usual starting dose is 400-600 mg per day during the first month. Following a favourable response to danazol, the lowest effective maintenance dose should be sought for a continuous preventive treatment by gradually decreasing the dosage in intervals of 1-3 months. The usual maintenance dose lies between 50 and 200 mg per day. Long-term prophylactic treatment in children should be avoided, in connection with possible hormonal effects of Danatrol.

4.3 Contraindications

- Pregnancy and lactation (see section 4.6 “pregnancy and lactation”)
- Markedly impaired hepatic, renal or cardiac function
- Porphyria
- Active thrombosis or thromboembolic disease or a history of such events
- Androgen-dependent tumours
- undiagnosed abnormal genital bleeding
- Hypersensitivity to any of the constituents of Danatrol
- Hepatocellular adenoma

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Danazol should only be prescribed by a specialist with experience in this area and after a careful diagnosis has been made.

Before starting treatment, pregnancy should be ruled out. In case of doubt a pregnancy test should be taken.
Oral contraceptives and other contraceptives on hormonal base should be stopped before starting the treatment. Danatrol does not inhibit the ovulation in all cases; for that reason complementary non-hormonal contraceptives have to be applied.

Symptomatic endometriosis and benign fibrocystic breast disease
It is advised to limit the duration of treatment to a maximum of 6-9 months (see also section 4.4.1 “Special warnings”). Partly due to the lack of information regarding the safety of long-term treatment with Danatrol it is recommended to initiate therapy only after clinical and possibly laparoscopic examination in which the necessity is clearly shown.

Hereditary angioneurotic edema
If Danatrol is used for longer (over 6 months) or repeated treatment, biannual hepatic ultrasonography is recommended. Laboratory monitoring including urine- and haematological analysis (including lipids and hepatic function) is recommended.

Before administration of Danatrol (hormone-dependent) malignancies should be ruled out.

4.4.1 Special warnings

Danazol should be stopped if any clinical significant adverse events arise, and particularly if there is evidence of:

- virilization, e.g. acne, greasy skin, hirsutism, weight increase, change of voice (for instance hoarseness, sore throat, or instability or lowering of the voice), clitoral hypertrophy and hair loss. Failure to discontinue danazol increases 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

- Thrombosis or thromboembolism

Since repeating a course of therapy may be necessary, care should be taken, as no safety data are available in relation to repeated courses over time. Long-term exposure to 17-alkylated steroids has been associated with severe toxicity including cholestatic icterus, hepatitis adenomata and hepatic peliosis. The risk of similar problems should be considered with Danatrol.

Data from two case-controlled epidemiological studies, were pooled to examine the relationship between endometriosis, endometriosis treatment and ovarian cancer. These preliminary results suggest that the use of danazol might increase the baseline risk of ovarian cancer in endometriosis-treated patients.

4.4.2 Precautions for use

Danatrol may cause fluid retention, particular care should be observed in using danazol in patients with:
- minor to moderate hepatic or renal disease
- minor to moderate cardiac insufficiency
- hypertension
- epilepsy
- migraine
- any state which may be exacerbated by fluid retention
- diabetes mellitus
- polycythemia
- hereditary or acquired lipoprotein disorder
- persistent androgenic reactions to previous gonadal steroid treatment

Before treatment initiation, the presence of hormone-dependent carcinoma should be excluded. Breast nodules should be checked for persistence or enlargement during danazol treatment in benign breast disease.

4.5 Interactions with other medicinal products and other forms of interaction
- anticonvulsive drugs: danazol can increase plasma level of carbamazepine and may affect responsiveness to this agent and to phenytoin. A similar interaction with phenobarbital is possible
- antidiabetic drugs: danazol can cause insulin resistance
- oral anticoagulants: danazol can potentiate the action of warfarin
- antihypertensive drugs: danazol can diminish the effectiveness of antihypertensive agents
- cyclosporine and tacrolimus: danazol can raise the plasma level of cyclosporine and tacrolimus, which may lead to an increase of the renal toxicity of these drugs
- concomitant steroids: interactions between danazol and gonadal steroid therapy are likely
- other drug interactions: danazol can increase the calcemic response to alpha calcidol in primary hyperparathyroidism
- interactions with laboratory function tests: Danazol treatment may interfere with laboratory determination of testosterone or plasma proteins (see section 4.8 “undesirable effects”). During treatment with danazol there is a clear decrease of serum thyroxin and thyroxin binding protein, which can lead to a falsely-positive diagnosis of hypothyroidism.

4.6 Pregnancy and lactation

Use during pregnancy:

Danatrol is contraindicated in pregnancy. Virilization of the female fetus, such as clitoral hypertrophy, labial hypertrophy, to complete pseudohermaphroditism, has been observed when danazol was used during pregnancy. The extent of the effect is dependent of duration of the treatment and the dosage.
Pregnancy should be excluded before the start of the therapy. An effective, non-hormonal method of contraception should be employed in women of childbearing age when using Danatrol(see section 4.4 “special warnings and precautions for use”).

Use during lactation:

No data are available about the use of Danatrol during lactation. Because of the theoretical potential for androgenic effects in breast-fed infants, Danatrol should not be given to lactating patients.

4.7 Effect on ability to drive and use machines.

Data are unknown. In connection with the possible appearance of the side effect of dizziness account should be taken into an influence on the driving ability and on the ability to handle machines.

4.8 Undesirable effects

The frequency of the hereafter mentioned undesirable effects are defined using the following convection : very common (≥1/10): common (≥ 1/100,<1/10); uncommon (≥1/1.000,<1/1.000); rare (≥1/10.000,<1/1.000); very rare (<1/10.000)
The incidence of adverse events seems to increase with longer duration of Danatrol use.

Blood and lymphatic system disorders
Rare: Increase in red cell and platelet count, polycythemia, leucopenia and thrombocytopenia
Very rare: Reversible erythrocytosis, eosinophilia, splenic peliosis

Endocrine disorders
Common:
Androgenic effects: acne, greasy skin, hirsutism, hairloss, voice change (e.g. hoarseness, sore throat or instability c.q. lowering of the voice)
Other endocrine effects: disturbance of the menstrual cycle such as intermenstrual spotting, shift of the cycle and amenorrhea, flushing
Rare:
Androgenic effects: clitoral hypertrophy, fluid retention

Metabolic and nutrition disorders
Common: Weight gain, increased appetite

Increased insulin resistance can occur in diabetes mellitus patients, but symptomatic hypoglycaemia has also been reported, as well as elevation of plasma glucagons levels and abnormal glucose tolerance.
A change in lipoproteins consisting of an increase in LDL cholesterol, a decrease in HDL cholesterol affecting all subfractions and a decrease in apolipoproteins AI and AII can be expected.
Danazol may cause induction of aminoevulinic acid (ALA) synthetase and therefore of porphyrin metabolism. Reduction in thyroid binding globulin and T4 with increased uptake of T3, but without disturbance of thyroid stimulating hormone or of free thyroxin index can be expected.

Nervous system disorders
Common: Emotional lability, anxiety, depressed mood, nervousness, headache
Rare: Dizziness, vertigo, fatigue, benign intracranial hypertension
Very rare: Aggravation of epilepsy (or reveal the condition in predisposed patients), provocation of migraine

Eye disorders
Rare: Visual disturbances such as blurring of vision or difficulty in focussing, difficulty in wearing contact lenses and refraction disorders requiring correction

Cardiac disorders
Very rare: Hypertension, palpitation, tachycardia, myocardial infarction

Vascular disorders
Very rare: Thrombosis including sagittal sinus, cerebrovascular thrombosis and arterial thrombosis

Respiratory, thoracic and mediastinal disorders
Very rare: Chest pain, interstitial pneumonitis

Gastrointestinal disorders
Common: Nausea, epigastric pain

Hepatobiliary disorders
Uncommon: Isolated increases in serum transaminase levels
Rare: Cholestatic jaundice, benign hepatitis adenomata, pancreatitis
Very rare: Hepatic peliosis and malignant hepatic tumor in long-term use

Skin and subcutaneous tissue disorders
Common: Rashes which may be maculopapular, petechial or purpuric and may be accompanied by fever. Facial oedema and photosensitivity
Uncommon: Urticaria
Very rare: Inflammatory erythematous nodules, altered skin pigmentation, exfoliative dermatitis and erythema multiforme

Musculoskeletal and connective tissue disorders
Common: Backache, muscle cramps (sometimes severe, sometimes with elevation of creatine phosphokinase levels), muscle tremors, fasciculation, joint pain and joint swelling
*Very rare:*Carpal tunnel syndrome

Renal and urinary disorders
Common: Hematuria with prolonged use in hereditary angioneurotic edema

Reproductive system and breast disorders
Common: Vaginal dryness, vaginal irritation, changes in libido
Uncommon: Reduction in breast size as a result of lowered estrogen levels
Very rare: Reduction in spermatogenesis

4.9 Overdose
Serious intoxications with Danatrol have not yet been reported. In case of overdosage with large quantities of Danatrol: give activated carbon and purge with sodium sulfate. Further treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Danatrol belongs to the pharmacotherapeutic group of the other sex hormones (G3H), antigonadotropins(GO3XA).

The action of danazol seems primarily to be based on the directly inhibiting action on the gonadotropin secretion and/or on the gonadotropic hormone releasing hormone secretion.
Because of the fact that the bloodlevels of the hypophyseal gonadotropins LH and FSH decrease, in the course of which particularly the peak values are suppressed, while sometimes the basal levels decline to low-normal values, the following symptoms appear in women: a suppression of the menstruation, ovulation inhibition, regressive change in the vaginal smear and atrophic changes in the endometrium. Danazol has no progestogen and oestrogen actions, but does possess some weak androgenous and anabolic properties. It does not seem to influence the other hypophyseal-endocrinic axes and the effect on circulating gonadotropins is obviously reversible, as these hormones regain their earlier levels after cessation of the treatment. As a rule the menstrual cycle is restored within 1-2 months after cessation of the treatment. Both humane pharmacological- and clinical studies with danazol confirm the antigonadotropic action.

5.2 Pharmacokinetic properties:

Absorption:
Danazol is absorbed from the gastrointestinal tract after which peak-plasmaconcentrations of 50-80 ng/ml are reached after about 2-3 hours. The bioavailability can be tripled by taking very fat food. The absolute bioavailability is not known as no intravenous form is available, but is less than 33%. After multiple administration of danazol (3 dd. 200 mg) the maximum level is an average of 238± 122 (s.d.) ng/ml (range 106-519). In multiple administration in the dosage area of 100 – 400 mg the absorptionkinetics are nearly linear.

Distribution:
In monkeys and rats higher concentrations than in plasma are only formed in the excretory organs (liver and kidney) and in the adrenal cortex.

Biotransformation:
Danazol is quickly and nearly completely metabolized in the liver. The two most important metabolites are 2-hydroxy-methylethisterone and ethisterone. These metabolites are not active. Before excretion conjugation takes place.

Elimination:
No data in man are known. From studies in monkeys it appeared that after 96 hours almost no danazol was excreted unchanged. Of the metabolites 36% is excreted by way of the urine and 48% by way of the faeces (biliary excretion).

Plasma-halflife:
After 1 single dose the plasma half-life varies between 3-6 hours.

Duration of the action:
After cessation of the danazol treatment it takes about 1-2 months before normal hormone levels return.

5.3 Preclinical safety data:

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Danatrol capsules of 100 and 200 mg contain as additives corn starch, lactose, talcum and magnesiumstearate. The capsule body contains titanium dioxide (E171) and gelatin.

6.2 Incompatibilities:

Not applicable.

6.3 Stability

5 years

6.4 Special precautions for storage:

Do not store above 25°C.

6.5 Nature and contents of container

1. Danatrol 100 mg is presented per 100 capsules in a glass bottle and strips.
2. Danatrol 200 mg is presented per 200 capsules in strips.

6.6 Directions for use/processing instructions

Not applicable

7. MARKETING AUTHORISATION HOLDER

sanofi-aventis Netherlands B.V.
Kampenringweg 45 D-E
2803 PE Gouda

8. MARKETING AUTHORISATION NUMBER(S)

100 mg capsules are registered under RVG 06982
200 mg capsules are registered under RVG 06983

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

October 1998

10. DATE OF REVISION OF THE TEXT

Last partial revision concerns section 7.

August 21, 2006.