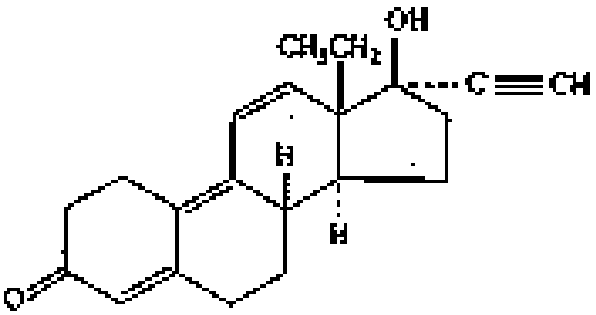
APPROVED PRODUCT INFORMATION
DIMETRIOSE® CAPSULES

DESCRIPTION

Each DIMETRIOSE capsule contains 2.5mg gestrinone. Gestrinone is a white to slightly yellow, crystalline powder. Its chemical name is 13β-ethyl-17α-ethynyl-17β-hydroxy-gona-4,9,11-trien-3-one. It is structurally related to norgestrel, differing only in having two extra unsaturated bonds at positions 9 and 11. The empirical formula for gestrinone is $C_{21}H_{24}O_2$. Its molecular weight is 308.4. The structural formula is as follows:



PHARMACOLOGY

Pharmacodynamics

Gestrinone is a synthetic steroid hormone with anti-progestin activity. *In vitro*, it has weak agonist activity on progesterone receptors in the rabbit endometrium and progesterone antagonist activity in various other pharmacological test systems.

In addition, it has moderate agonist activity on prostatic androgen receptors *in vitro*. In various *in vivo* test systems this activity was found to be low.

Thus gestrinone has a weak androgen and progestogen activity. Its main action is on the hypothalamic-pituitary axis where it inhibits gonadotrophin release with a weak inhibitory effect on synthesis. It also possesses anti-oestrogen activity.

The suppression of the ovular gonadotrophin peak is observed after the first month of treatment; the resulting absence of ovarian secretion rapidly leads to endometrial atrophy.

Apart from its anti-hypophyseal action, gestrinone also has anti-progesterone activity on cell receptors in both endometrium and extra-uterine ectopic implants.

Moreover, gestrinone has no specific oestrogen and/or uterotrophic activity, nor any activity on the adrenal gland.

No antiglucocorticoid activity has been detected in animal studies.

Pharmacokinetics

Linear pharmacokinetics are found after oral administration of doses of 1.25mg, 2.5mg or 5mg.

The average peak plasma concentration is 19 ng/mL and occurs two hours after administration of a single 2.5mg capsule.

The plasma elimination half-life and the volume of distribution are approximately 27 hours and 67 litres respectively. Gestrinone binds to plasma albumin.

Three days after administration, plasma levels of gestrinone are only 5% of the peak plasma concentration. The steady state is reached after the second capsule, which is taken three days after the first.

In the normal therapeutic regimen, there is, therefore, no risk of accumulation.

No data are available on the effect of renal impairment.

An absolute bioavailability study in a healthy adult showed that gestrinone is completely absorbed after oral administration and that there is a negligible first pass effect.

Gestrinone is actively metabolised in the liver, essentially by hydroxylation, to conjugated metabolites 16b-hydroxy,13-ethyl (1-OH) and D-homo gestrinone. In vitro studies have shown that the metabolites are active but weaker than the unchanged drug. About 40-45% of a dose is excreted in the urine and 30-35% in the faeces.

There is no information about the effect of food on the bioavailability of gestrinone.

INDICATIONS

Mild to moderate endometriosis with or without accompanying sterility. Treatment is limited to a single course of six months duration per lifetime.

CONTRAINDICATIONS

- Pregnancy
- Lactation
- Severe cardiac, renal or hepatic insufficiency
- Metabolic or vascular disorders, including vascular disorders during previous oestrogen and/or progestogen therapy.

WARNINGS AND PRECAUTIONS

Treatment with DIMETRIOSE must be started on the first day of a menstrual cycle. Pregnancy must be excluded before starting treatment (see "Use in Pregnancy" section). A barrier contraceptive method must be used during treatment.

Gestrinone may occasionally cause some degree of fluid retention. Patients with cardiac or renal dysfunction require close monitoring.

Monitor ALAT, ASAT and cholesterol fractions in hyperlipidaemic subjects and blood sugar levels in diabetics.

Gestrinone will cause a decrease in the concentration of thyroid-binding globulin. Hence there will be a decrease in serum total thyroxine levels. This is without clinical significance as free thyroxine levels remain within the reference range as do thyroid-stimulating hormone levels.

DIMETRIOSE is not recommended for elderly patients or for children.

Patients should be watched closely for signs of androgenic effects, some of which may not be reversible (see Adverse Reactions).

Use in Pregnancy - Category D

Gestrinone is contraindicated in pregnancy as it may interfere with pregnancy and, in animal tests, it caused masculinisation of female fetuses. Gestrinone inhibits ovulation in many women but pregnancies can occur if barrier contraception is not used. Therefore gestrinone must not be relied on for contraception and it is essential that barrier methods of contraception are used throughout treatment.

Use in Lactation

It is not known whether gestrinone is excreted in human milk. As a related compound (norgestrel) is excreted in milk, gestrinone must also be considered capable of passing into milk. Because of potential androgenic effects on the infant, gestrinone is contraindicated during lactation.

Drug Interactions

Concomitant administration of anti-epileptic drugs or rifampicin may result in accelerated metabolism of gestrinone.

ADVERSE REACTIONS

The majority of adverse events have been associated with the slight androgenic activity of gestrinone. This has resulted in a fairly high incidence of reported events. In almost every case, the symptoms regressed after completion of treatment.

The following adverse reactions were reported in a multicentre, six month study comparing gestrinone with danazol in a total of 269 patients.

More Common Reactions

Acne, seborrhoea, hirsutism, voice changes, weight increase, hot flushes, headache, lethargy, depression, dizziness, irritability, paraesthesia, sweating, nausea, abdominal pain/swelling, increased appetite, abdominal discomfort, discomfort, constipation, cramps, back pain, generalised aches and cramps, arthralgia, pruritus, dry skin, skin rash, loss of libido, feeling hot, feeling unwell, eye problems, vulva and vaginal bleeding, irregular bleeding, breast pain/ache, heavy bleeding, frequent menses, micturition problems, pelvic pain.

Less Common Reactions

Blurred vision, anxiety, forgetfulness, faintness, flashing lights, shakiness, indigestion, diarrhoea, vomiting, iliac fossa pain, stomach upset, anal irritation, thirstiness, weight loss, loin pain, head/neck pains/cramps, oedema, pressure in limbs, tightness and numbness in hands, dry scalp, eczema, hair loss, face redness, pigmentation of neck and skin, general skin problems, styes, dysmenorrhoea, reduction in breast size, premenstrual syndrome, Candida vaginitis, post-coital bleeding, rectal bleeding, breast lumps, nipple tenderness, continuous bleeding, dyspareunia, light period, chest pain, breathlessness, chest infection, chest tenderness, sneezing, mouth problems, varicose veins.

The following table is compiled from the results of the abovementioned clinical trial:

SYMPTOM	TREATMENT GROUP					
	GESTRINONE			DANAZOL		
	Number of patients reporting pre-treatment	At least once during treatment / patients who start treatment	For the first time during treatment / patients without symptom pre-treatment, and who start treatment	Number of patients reporting pre-treatment	At least once during treatment / patients who start treatment	For the first time during treatment / patients without symptom pre-treatment and who start treatment
Acne	26/131 (20%)	100/129 (78%)	72/98 (73%)	26/133 (20%)	84/130 (65%)	62/105 (59%)
Seborrhoea	44/131 (34%)	79/129 (61%)	43/85 (51%)	54/133 (41%)	57/130 (44%)	19/77 (25%)
Hirsutism	18/131(14%)	71/129 (55%)	58/111 (52%)	24/133 (18%)	43/130 (33%)	29/106 (27%)
Voice problem	3/131 (2%)	15/129 (12%)	14/126 (11%)	4/133 (3%)	19/130 (15%)	18/126 (14%)
Swelling of ankles/feet	17/131 (13%)	47/129 (36%)	37/113 (33%)	19/133 (14%)	43/130 (33%)	29/111 (26%)
Hot flushes	31/131 (24%)	67/129 (52%)	41/98 (42%)	25/133 (19%)	66/130 (51%)	47/106 (44%)
Sweating problems	26/131 (20%)	69/129 (53%)	47/103 (46%)	15/133 (11%)	53/130 (41%)	43/116 (37%)
Loss of Libido	39/130 (30%)	61/127 (48%)	35/89 (39%)	45/132 (34%)	54/129 (42%)	28/84 (33%)
Reduction in breast size	-	51/129 (40%)	-	-	66/130 (51%)	-
Leg cramp	27/130 (21%)	50/129 (39%)	36/103 (35%)	32/133 (24%)	73/130 (56%)	51/99 (52%)
Headaches	72/130 (55%)	90/129 (70%)	33/58 (57%)	60/133 (45%)	81/130 (62%)	35/72 (49%)
Nausea	30/130 (23%)	85/129 (66%)	64/100 (64%)	27/133 (20%)	76/130 (58%)	57/104 (55%)
Vomiting	12/130 (9%)	15/129 (12%)	12/117 (10%)	12/133 (9%)	22/130 (17%)	17/119 (14%)
Loss of Appetite	14/130 (11%)	33/129 (26%)	27/115 (23%)	11/133 (8%)	26/130 (20%)	23/119 (19%)
Hunger	28/130 (21%)	75/129 (58%)	54/101 (53%)	25/133 (19%)	89/130 (68%)	69/105 (66%)
Dizziness/Giddiness	29/130 (22%)	58/129 (45%)	38/100 (38%)	31/133 (23%)	49/130 (38%)	33/100 (33%)
Tiredness	71/130 (54%)	102/129 (79%)	44/59 (75%)	64/133 (48%)	100/130 (77%)	45/67 (67%)
Faintness	11/130 (8%)	16/129 (12%)	13/118 (11%)	14/133 (11%)	18/130 (14%)	11/116 (9%)
Skin Rash	18/130 (14%)	31/129 (24%)	26/111 (23%)	12/133 (9%)	24/130 (18%)	18/119 (15%)

Clinical Laboratory Test Findings:

A clinical study showed a significant decrease in HDL cholesterol during treatment. Small increases in red cell count and haemoglobin have been observed.

DOSAGE AND ADMINISTRATION

A barrier contraceptive method must be used for the entire duration of treatment.

DIMETRIOSE is for oral administration only. The recommended dosage is one capsule twice a week. **The first dose should be taken on the first day of a menstrual cycle.** The second dose should be taken three days later. Thereafter, DIMETRIOSE capsules should be taken on the same two days of the week (preferably at the same time of day) every week for the duration of treatment, which should last for six months without interruption. No repeat courses should be undertaken.

Depending on the judgement of the physician, the dose can be increased to three capsules per week for several weeks, especially when spotting occurs.

In case of missed medication

If one dose is missed, a capsule should be taken as soon as possible and the original sequence continued.

If two or more doses are missed, treatment should be stopped and therapy re-started on the first day of the next menstrual cycle, following a negative pregnancy test and according to the usual dosage schedule.

OVERDOSAGE

In case of overdose, gastric lavage is recommended.

PRESENTATION

White hard gelatin capsules containing 2.5mg gestrinone. Each pack contains a blister strip of 8 capsules.

NAME AND ADDRESS OF SPONSOR
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