Progest 200

Micronized Progesterone

Soft capsules

Made in Argentina
Sale under prescription

Composition:
Each capsule of Progest 200 contains: Micronized progesterone 200 mg.
Excipients: Soybean lecithin 26.4 mg; mixture of saturated fatty acids triglycerides/ soybean oil (60:40 p/p) 50.0 mg; corn oil 263.6 mg.

Therapeutic Action:
Progestational therapy.

Indications:
Prevention of endometrial hyperplasia in women with uterus under estrogenic treatment for menopause.
Secondary amenorrhea.

Pharmacological action:
Progest 200 is an oral form of micronized progesterone, which is chemically identical to the ovarian progesterone.

Pharmacokinetics:
~ *Absorption*. After oral administration, the maximum serum concentration (C_{max}) is obtained within 3 hours.
The following data show the mean of pharmacokinetic parameters in post-menopause women after five days of treatment: C_{max} 38,1 ± 37,8 ng/ml; maximum time in which C_{max} is obtained (T_{max}) 2,3 ± 1,4 h; Area Under the Curve (AUC) 101,2 ± 66,0 ng hr/ml. Serum concentrations are linear and proportional to the dose, in an administration range of 100 mg to 300 mg/day in post-menopausal women.

~ *Distribution*. Progesterone binds between 96 and 99% to serum proteins, mainly to albumin (about 50 %), but it also binds to transcortin (43 to 48 %).

~ *Metabolism*. It is metabolized mainly in the liver to pregnanediols and pregnenolones. These are conjugated in the liver to glucuronides and sulfates. The metabolites excreted by the bile may be deconjugated afterwards and metabolized by the intestine by means of reduction and other processes.

~ *Excretion*. The pregnanediols and pregnenolones conjugates are excreted by the bile; afterwards may suffer an enteropathic recycling process or be eliminated by feces.

~ *Special Problems*. The micronized progesterone pharmacokinetic has not been assessed in obese or in low weight people.

~ *Race*. There is not enough information to compare the pharmacokinetics in different racial groups.

~ *Hepatic Impairment*. There have been no studies aimed at evaluating the liver disease effect in the progesterone availability. Anyway, since it is widely metabolized by the liver, its use in patients suffering from severe liver disease is contraindicated. In case a treatment is indicated for patients with mild or moderate liver disease, it must be carefully monitored.

~ *Renal Impairment*. There have been no studies to evaluate the renal disease in the progesterone availability. Due to the fact that metabolites are eliminated mainly by the kidney, *Progest 200* must be carefully used and only under strict control in patients suffering from renal impairment.

Dosage and Administration:
Prevention of endometrial hyperplasia.
One oral daily capsule, administered at night during 12 consecutive days in a sequential schedule for 28 days to menopausal women with uterus receiving estrogens.

Secondary amenorrhea.
Two capsules together daily, administered during the night for 10 days.

Contraindications:
Hypersensitivity to any of the components. Pregnancy. Thrombophlefibitis. Thromboembolic disorders. Cerebrovascular accident or patients with history of these conditions. Severe liver disease. Genital or mammary neoplasia. Non-diagnosed Vaginal bleeding. Abortion. As a diagnostic test for pregnancy.
This product contains peanut oil and therefore it must not be used in patients allergic to peanut.

Warnings:
One should be alert upon early manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular accident, pulmonary thromboembolism, retinal thrombosis). In these cases, treatment should be immediately discontinued. Treatment should also be discontinued if there is a sudden partial or complete vision loss or if there appears diplopia or migraine. Should the test show papilla edema or retinal vascular injury, the medication must be definitely suspended. It must be taken into account that in breast-feeding women, the administration of any drug must be performed when strictly necessary, since many pharmacological compounds are excreted in milk. Progestagens have been identified in the milk of the mothers that received said compounds. Their effect in nursing children has not been determined. Retrospective morbidity and mortality studies in Great Britain and morbidity studies in the United States showed a significant association between thrombophlebitis, pulmonary embolism, thrombosis and cerebral embolism and the use of oral contraceptives. The American study indicated that the risk does not persist after discontinuation and it is neither increased by administration over time.

Precautions:
General.
Before initiating the treatment, patients must undergo a physical examination that includes mainly mammary, genital and Papanicolau tests-
Since progesterone may cause certain degree of hydric retention, it is required that special attention be taken for that situations that may be influenced by this cause as epilepsy, migraine, asthma, cardiac or renal impairment.
In any case of irregular vaginal bleeding, non-functional causes must be considered. An adequate diagnosis should be tried in these patients. Those patients with history of depression should be controlled and discontinue the treatment if symptoms recur. It is unknown the influence of a prolonged treatment with a progestagen on hypophysis, ovarian, adrenal gland, liver and uterus functions. Although concomitant use of estrogens and micronized progesterone does not result in a decrease of the glucose tolerance, diabetic patients should be carefully monitored. The pathologist physician must be informed about the treatment upon receiving samples for their study. Due to the chance of developing thrombotic disorders in patients receiving combinations of estrogens and progestagens, the physician must be alert upon first manifestations of these phenomena. Some patients may experience dizziness or transient vertigo. Therefore, patients should be careful upon driving cars or machinery. A small number of women may suffer somnolence, dizziness, and important vertigo. It is advisable for these women the night administration, at bedtime.

Laboratory tests.
Some clinical studies results may be modified due to the combined use of estrogens and progestagens:
- Increase in sulfobromophthalein retention and other liver functions.
- *Coagulation test:* increase of VII, VIII, IX and X factors.
- Metapyrone test.
- Pregnanediol determination.
- *Thyroid function:* PBI increase, and the iodide bound to proteins. T3 decrease.

In patients (n=120) receiving a micronized progesterone schedule of 200 mg/day during 12 days in combination with conjugated estrogens 0,625 mg/day during 28 days per cycle an oral test was carried out as regards glucose tolerance where it was found that: insulin plasma levels at 2 hours decreased from baseline value, while glucose values increased slightly. There were no modifications as regards fibrinogen levels.

Carcinogenesis, mutagenesis, fertility decrease.
Progesterone has not been evaluated for carcinogenesis in animals, by oral administration. Implants in female rats produced breast cancer, granulosa tumors and endometrial sarcoma. In dogs, intramuscular injections for a prolonged time produced node hyperplasia and benign and malignant breast tumors. SC or IM injections of progesterone decreased the latency period and increased the incidence of breast tumors in rats previously treated with a chemical carcinogen.
Progesterone did not show evidence of genotoxicity in in vitro studies for mutations o chromosomal damage. In vivo studies for chromosomal damage in mice reached positive results in oral doses of 1000 mg/kg and 2000 mg/kg. Exogenous administration of progesterone showed an ovulation inhibition in several species and it is expected that high doses during a long period of time might reduce fertility until treatment is discontinued.

Pregnancy. Category B.
Reproductive studies have been carried out in mice at doses up to 9 times the oral dose in humans, in rats up to 44 times the oral dose, in rabbits at doses of 10 mcg/day locally released inside the uterus, in pigs at doses that are the half of the one administered to humans, and in rhesus monkeys about the same dose used for humans (all the doses based on body surface). The studies revealed a small or null fertility decrease or fetal damage. Several studies in women exposed to progesterone did not show increases as regards fetal malformations. The only case of cleft palate was observed in one child whose mother used micronized progesterone in the first period of pregnancy, although a definitive causal relationship has not been established. Fetal deaths cases have been rarely reported in women that received progesterone in indications not approved. Due to the fact that studies in humans do not may exclude the possibility of harm, micronized progesterone should be used during pregnancy only if indicated.

Breastfeeding.
The administration of any drug in nursing women must be performed only when it is strictly necessary, since many of the drugs are excreted in the milk. A certain quantity of Progestagens has been detected in the milk of the mothers that received it. The effect on nursing children has not been established.

Pediatric use.
Safety and efficacy of micronized progesterone activity in pediatric patients has not been established.

Interactions:
The progesterone metabolism by the hepatic microsomes was inhibited by ketoconazole. This is a known inhibitor of P450 3A4 cytochrome and therefore this suggests that this one or other known inhibitors of this enzyme may increase the progesterone bioavailability. The relevance of these "in vitro" findings is unknown.
Concomitant administration of conjugated estrogens to 29 menopausal women with micronized progesterone during a 12-day period resulted in an increase of the total estrone and equilin concentration and a decrease in the concentration of 17 beta estradiol. Half-life of conjugates estrogens was similar to the co-administration of micronized progesterone.

Adverse reactions:
Most common adverse reactions reported in ≥ 5% of patients were: dizziness (16 %), chest pain (11 %), headache (10 %), abdominal pain (10 %), fatigue (9 %), viral infections (7 %), abdominal distention (6 %), muscle pain (6 %), depression (6 %), irritation (5 %), respiratory upper tract infection (5 %).

Other adverse reactions reported in ≥ 5 % of patients were:
- *Autonomous nervous system:* dry mouth.
- *General:* Accidental injuries, chest pain, fever.
- *Cardiovascular system:* hypertension, palpitations, chest angina.
- *Peripheral and Central Nervous System:* Confusion, somnolence, speech problems.
- *GI System:* Constipation, dyspepsia, gastroenteritis, rectum hemorrhage, hiatal hernia, vomiting.
- *Auditory:* Ear pain.
- *Metabolism:* General or peripheral edema.
- *Musculoskeletal:* Arthritis, leg cramps, hypertonia, muscle malaise, myalgia.
- *Psychic:* Anxiety, lack of concentration, insomnia, personality disorders.
- *Reproductive System:* leukorrhea, uterine fibroma, vaginal dry, vaginal mycosis, vaginitis.
- *Immune System:* abscess, herpes simplex, lymphadenopathy.
- *Respiratory System:* Bronchitis, nose congestion, pharyngitis, pneumonitis, sinusitis.
- *Dermal:* Acne, verrucae, blisters.
- *Urinary System:* Urinary tract infection.
- *Vision:* Abnormal vision.

The following adverse experiences were also reported: sweating increase, asthenia, dental disorders, anorexia, appetite increase, nervousness, mammary increase, reversible hepatitis and transaminase value elevations. These events occurred mainly in patients who received high doses of up to 1200 mg.

The following adverse events were observed in women who received progestagens in general: bleeding due to disruption, small blood stains, changes in menstrual flow, amenorrhea, changes in body weight (increase or decrease), changes in the cervical epithelium joint and secretion, cholestatic jaundice, anaphylactoid reactions and anaphylaxis, rash (allergic) with or without itching, melasma or chloasma, pyrexia and insomnia.

Keep this and all medications out of the reach of children.

Overdose:
No cases of non-treated overdose have been so far reported.
Should there be an overdose, attend the nearest Hospital or call the Toxicology Centers.

How supplied:
Progest 200 is supplied in packages that contain 15 soft capsules.

Keep in a dry place at a temperature between 8 and 20 °C.

Reg. N°: 43.560
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