

MEGESTROL SERVYCAL
MEGESTROL ACETATE 160 mg

Tablets

Sale under filed prescription

Made in Argentina

Quali-quantitative composition:

Each tablet contains:

Megestrol acetate	160.00 mg
Lactose	73.00 mg
Microcrystalline cellulose	140.00 mg
Hydroxypropyl methylcellulose	2.00 mg
Glycerol polyethylene glycol oxystearate	2.00 mg
Croscarmellose sodium	20.00 mg
Magnesium stearate	3.00 mg
Purified water	110.00 mg

Category:

Megestrol acetate is a synthetic drug with an antineoplastic and progestational action.

Indications:

Megestrol acetate is indicated for the palliative treatment of advanced of carcinoma of the breast and endometrium (recurrent, advanced, or metastatic disease).

It should not be used in lieu of currently accepted therapeutic procedures such as surgery, radiotherapy or chemotherapy.

Pharmacology:

Pharmacodynamics:

The precise mechanism by which Megestrol carries out its antineoplastic action against breast and endometrial carcinoma is unknown at present. However, it is known that this drug inhibits the production of gonadotropin in the pituitary gland, thus directly decreasing estrogen secretion. This mechanism may be one of the factors of megestrol's action. Evidence suggests that this drug has a local effect as a result of the marked changes produced by the direct instillation of progestational agents into the endometrial cavity.

The antineoplastic action of megestrol acetate on carcinoma of the breast is exerted by modifying the action of other steroid hormones and by producing a direct cytotoxic effect on tumor cells. In metastatic cancer, hormone receptors may be present in some tumors but not in others.

The receptor mechanism is a cyclic process whereby the estrogen produced by the ovaries enters the target cells, forms a complex with the cytoplasmic receptor and is transported into the cell nucleus. There it induces gene transcription and it leads to an alteration of normal cell functions.

At pharmacological doses, megestrol acetate not only reduces the number of hormone-dependent human breast carcinoma cells but is also capable of modifying or abolishing the stimulatory effects of estrogen on these cells. This has been suggested as a mechanism by which progestins may inhibit in one of two ways: by interfering with the stability, availability, or turnover of the estrogen receptor complex in its interaction with genes or in conjunction with the progestin receptor complex, or by directly interacting with the genome to turn off specific estrogen-responsive genes.

Pharmacokinetics:

The analytical methods used to determine the megestrol plasma levels include the following: mass fragmentography, gas chromatography, HPLC, and radioimmunoassay. The plasma levels of megestrol are dependent not only on the method used but also intestinal and hepatic inactivation of the drug, which may be affected by factors such as intestinal tract motility, intestinal bacteria, antibiotics administered, body weight, diet, and liver function.

Metabolites account for 5% to 8% of the administered dose; this amount was considered to be negligible. The primary route of elimination is the urine. When radiolabeled megestrol acetate was administered to humans at doses of 4 mg to 90 mg, the urinary excretion within 10 days of administration ranged from 56.5% to 78.4%, with a mean value of 66.4%; and fecal excretion ranged from 7.7% to 30.3%, with a mean value of 19.8%. Total recovered radioactivity ranged from 83.1% to 94.7%, with a mean value of 86.2%.

The respiratory excretion measured as labeled carbon dioxide and fat storage accounted for a minimum part of the radioactivity not found in urine and feces. Plasma levels of the drug assayed by HPLC showed peak levels for the first administered 40 mg that ranged from 10 to 56 ng/mL, with a mean value of 27.6% ng/mL, and the times to peak concentrations ranged from 1.0 to 3.0 hs, with a mean value of 2.2 hs.

Plasma elimination half-life ranged from 13.0 hs to 104.9 hs, with a mean value of 34.2 hs.

Dosage and Administration:

Megestrol acetate should be administered in divided doses according to the disease.

- Breast cancer: 160 mg/day q.i.d.
- Endometrial carcinoma: 40-320 mg/day divided in several doses.

At least continuous treatment of 2 months (minimum adequate period) is necessary to establish the efficacy of megestrol treatment.

Contraindications: hypersensitivity to megestrol acetate or any excipient of the composition.

Warnings:

Megestrol acetate may cause fetal harm when administered to a pregnant woman. Fertility and reproduction studies with high doses of megestrol acetate have shown a reversible feminizing effect on some fetuses of male mice. There are no adequate and well-controlled studies in pregnant women at present. If this medicine is used during pregnancy, or if the patient becomes pregnant while receiving medicine, the patient should be advised of the potential hazard to the fetus.

Women of childbearing potential should be advised of this hazard by the physician in order to take the necessary preventive measures to avoid becoming pregnant.

The use of megestrol is not recommended for the treatment of other neoplastic diseases. The glucocorticoid activity of megestrol acetate has not been fully evaluated; however, an adrenal suppression has been observed.

New clinical cases of type 2 diabetes mellitus or exacerbation of pre-existing diabetes, and Cushing's syndrome have been reported in direct connection with the use of megestrol acetate.

Besides, some clinical cases of apparent adrenal insufficiency have been reported in association with the use of megestrol acetate.

The possibility of adrenal suppression should be considered in patients receiving chronic megestrol, or patients who have been withdrawn from megestrol after a long treatment and who show symptoms such as hypotension, nausea, vomits, weakness, or dizziness.

Laboratory evaluation for adrenal insufficiency and replacement by stress doses of rapidly acting glucocorticoid may be recommended in some patients.

The hypothalamic-pituitary-adrenal insufficiency may result in death.

Precautions:

- *General:* Patients treated for recurrent or metastatic cancer should be closely monitored. This medicine should be used with caution in patients with a history of thromboembolic disease.
- *Use in diabetics:* exacerbation of pre-existing diabetes with increased insulin requirements has been reported in association with the use of megestrol acetate.
- *Laboratory tests:* breast malignancies in which estrogen or progesterone receptors are positive are more likely to respond to megestrol acetate treatment.
- *Carcinogenesis, Mutagenesis and Fertility Impairment:* The administration of megestrol acetate to female dogs for more than 7 years was associated with an increased incidence of benign and malignant breast tumors. Comparable studies in rats and monkeys have not shown an increased incidence of tumors. The relationship of dog tumors to human tumors is unknown but it should be considered in assessing the risk-benefit ratio when prescribing this medicine. Besides, patients receiving megestrol should be closely monitored.
- *Pregnancy:* this medicine should be considered to be Pregnancy Category D.
- *Breastfeeding:* Due to the adverse effects that this medicine may have on newborns, breastfeeding should be discontinued if megestrol is required to treat the breastfeeding mother's cancer.
- *Pediatric use:* the safety and efficacy of megestrol in this type of patients have not been established.

Adverse Reactions:

- *Weight gain:* this is a frequent effect of megestrol acetate. This gain has been associated with increased appetite and is not necessarily associated with fluid retention.
- *Thromboembolic phenomena:* thromboembolic phenomena including thrombophlebitis and pulmonary embolism, in some cases fatal, have been reported.
- **Other adverse reactions:** Heart failure, nausea and vomiting, edema, breakthrough menstrual bleeding, dyspnea, tumor flare with or without hypercalcemia, hyperglycemia, glucose intolerance, alopecia, carpal tunnel syndrome, mood changes, hot flashes, hypertension, asthenia, upset, lethargy, sweating, and rash.

Overdosage:

No serious or unexpected local side effects have been shown in studies involving megestrol acetate at high doses such as 1,600 mg/day. The oral administration of high doses of megestrol acetate (5 g/kg) produced no toxic effect on mice.

Megestrol acetate has not been tested for dialysis; however, because of its low solubility it has been postulated that this would not be an effective method to treat an overdose.

In the case of acute poisoning, go to the nearest Hospital or contact Toxicology Centers:

Hospital de Niños Dr. Ricardo Gutiérrez: Ph: + 54 (11) 4962-6666 / 2247

Hospital Dr. Juan P. Garrahan: Ph: + 54 (11) 4941-6191 / 6012

Hospital Dr. Juan A. Fernández: Ph: + 54 (11) 4801-5555

Hospital A. Posadas: Ph: + 54 (11) 4654-6648 / 4658-7777

- **Patient information:** patients treated with megestrol acetate should receive the following instructions from their doctors:
 1. This medicine must be used under strict medical supervision.
 2. Patients should inform their doctors if they experience any adverse reaction while taking this medicine.
 3. If you miss a dose, never double it to make up for the missed dose. Consult your doctor and follow his/her directions carefully.

Presentations: carton containing 30 tablets.

KEEP AT ROOM TEMPERATURE BELOW 40° C AND PROTECT FROM LIGHT.

THIS MEDICINE SHALL BE USED UNDER MEDICAL PRESCRIPTION AND SURVEILLANCE, AND IT SHALL NOT BE REPEATED WITHOUT A NEW

PRESCRIPTION.

KEEP OUT OF THE REACH OF CHILDREN

Medicinal Specialty Authorized by the Argentine Ministry of Health (A.N.M.A.T.)

Certificate No. 42899

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Revision date: 09/2003.