PRODUCT MONOGRAPH

MEGESTROL

Megestrol Acetate Tablets USP

40 mg and 160 mg

Progestogen / Antineoplastic / Antianorexic / Anticachectic

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PHARMACOLOGICAL CLASSIFICATION

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ACTIONS AND CLINICAL PHARMACOLOGY

The precise mechanism of action by which megestrol acetate produces its antineoplastic effects is unknown at present. Pharmacologic doses of megestrol acetate exerted a direct cytotoxic effect on human breast cancer cells *in vitro* and proved capable of modifying and abolishing the stimulatory effects of estrogen on breast cancer cell lines.

Megestrol acetate interacts with progesterone receptors to stimulate cell maturation through a progestin–inducing mechanism. It has also been shown to have certain androgenic properties and may also modify glucocorticoid action by binding to the glucocorticoid receptor.

In previously untreated breast cancer patients with ER^+ PR^+ receptor status, endocrine therapy has been shown to produce responses in up to 81% of patients.

Inhibition of persistent endometrial hyperplasia and of persistent endometrial adenocarcinoma was observed upon administration of megestrol acetate in doses of 160 mg/day and megestrol acetate partially inhibited expression of estrogen dependent secretory proteins and certain constituent proteins in the rat uterine epithelium.

Metastatic carcinoma of the prostate responds to a variety of hormone manipulations that decrease the level of androgens in androgen–sensitive tissue. The primary mechanism of action of megestrol acetate and DES is the suppression of luteinizing hormone from the pituitary gland, which leads to suppression of serum androgens arising from the testicle.

Megestrol acetate may have other mechanisms of action as well, including an antiandrogen activity, suppression of adrenal androgens, and possibly the inhibition of enzymes, eg. 5 α–reductase, critical to androgen metabolism within the prostate. The precise mechanism of action by which megestrol acetate produces its antianorexic and anticachectic effects is also unknown at present. The gain in weight associated with megestrol acetate is associated with increased appetite, an increase in fat and body cell mass.

Pharmacokinetics

In 24* healthy male volunteers (age 19-44 years) who received 160 mg of megestrol acetate given as a 40 mg q.i.d. regimen, the oral absorption of megestrol acetate appeared to be variable. Peak drug levels for the first 40 mg dose ranged from 10 to 56 ng/mL (mean 27.6 ng/mL) and the times to peak concentrations ranged from 1.0 to 3.0 hours (mean 2.2 hours). Plasma elimination half–life ranged from 9.9 to 104.9 hours (mean 34.2 hours). The steady state plasma concentrations for a 40 mg q.i.d. regimen have not been established.

Estimates of plasma levels of megestrol acetate are dependent on the measurement method used. Plasma levels depend on intestinal and hepatic inactivation of the drug, which may be affected by intestinal tract

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* Pharmacokinetic data from one patient excluded due to unusually high drug levels.

mobility, intestinal bacteria, concomitant antibiotic administration, body weight, diet and hepatic function.

Pharmacodynamics

A single oral dose of radioactive megestrol acetate given to one male produced a maximum blood level in one to three hours and gradually fell over a 24–hour period. Megestrol acetate when given orally to women exhibited an average excretion of 86.2% (range 83.1% to 94.7%), fecal excretion accounted for 19.8% (range 7.7% to 30.3%) and urinary excretion for 66.4% (56.5% to 78.4%). The biological half–life for doses of 60–90 mg was 3.5 days. The half–life of a 160 mg dose was 37.6 hours. The excretion occurred as three glucuronide conjugates with hydroxylation occurring at either the 2–α, or the 6–methyl position or at both positions. Other metabolites occur but only account for 5-8% of the dose.

Respiratory excretion and fat storage may account for the fraction of an administered dose not found in urine or feces.

Comparative Bioavailability

A two–way, single–dose, randomized crossover bioavailability study was conducted in 32 healthy male volunteers to evaluate the relative bioavailability of MEGESTROL 160 mg tablets (manufactured by AA Pharma Inc.) against Megace® 160 mg tablets (Bristol Laboratories). There were 30 subjects plus two alternate subjects. Subjects 1 through 30 were randomized. Thirty–one subjects completed the entire clinical portion of the study. The mean pharmacokinetic results from 30 subjects are presented below. The data of alternate Subject 31 replaced the data of Subject 08, who did not complete the study.

Parameter	Geometric Mean* Arithmetic Mean** (CV%)		Ratio of Means (%)
	Megestrol	Megace®	
AUC_{0-72} (ng.hr/mL)	1794 1992 (49)	1628 1815 (52)	110.2
AUC_T (ng.hr/mL)	2046 2313 (52)	1808 2084 (61)	113.2
AUC_I (ng.hr/mL)	2266 2596 (55)	2097 2448 (70)	108.1
C_{max} (ng/mL)	96 109 (57)	102 112 (43)	94.1
T_{max} (hr)	3.6 (1.6)	3.6 (1.7)	-
$t_{1/2}$ (hr)	34.1 (14.1)	39.2 (32.1)	-

* The geometric means are presented for AUC_{0-72}, AUC_T, AUC_I and C_{max} parameters
**For T_{max} and $t_{1/2}$ parameters, the arithmetic means (SD) are presented

INDICATIONS AND CLINICAL USE

MEGESTROL (megestrol acetate) is indicated for adjunctive or palliative treatment of recurrent, inoperable or metastatic carcinoma of the breast and endometrium and for palliative treatment of hormone responsive advanced (Stage D_2) carcinoma of the prostate. MEGESTROL should not be used in lieu of currently accepted procedures such as surgery and radiation. Objective or subjective responses or arrest of tumour growth may occur for one to several months while on therapy.

MEGESTROL is also indicated in male or female patients for the treatment of anorexia, cachexia or weight loss secondary to metastatic cancer.

CONTRAINDICATIONS

MEGESTROL (megestrol acetate) is contraindicated in those people who are sensitive to megestrol acetate or any ingredients in the dosage form. It should not be used as a diagnostic test for pregnancy.

WARNINGS

The use of progestational agents during the first four months of pregnancy is not recommended.

Progestational agents have been used beginning within the first trimester of pregnancy in an attempt to prevent habitual abortion or treat threatened abortion. There is no adequate evidence that such use is effective and there is evidence of potential harm to the fetus when such drugs are given during the first four months of pregnancy. Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine–relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but insofar as some of these drugs induce mild virilization of the external genitalia of the female fetus, and because of the increased association of hypospadias in the male fetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy.

If the patient is exposed to MEGESTROL (megestrol acetate) during the first four months of pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General

Therapy with MEGESTROL (megestrol acetate) for weight loss should only be instituted after treatable causes of weight loss are sought and addressed. These treatable causes include possible malignancies, systematic infections, gastrointestinal disorders affecting absorption, endocrine disease and renal or psychiatric disease.

Use megestrol acetate with caution in patients with a history of thrombophlebitis. Close, customary surveillance is indicated as in any patient being treated for recurrent or metastatic cancer. Patients receiving large doses of progestational agents such as megestrol acetate continuously for prolonged periods should be observed closely for possible adrenal cortical suppression.

Use in Children

Safety and effectiveness in children have not been established.

Nursing Mothers

Because many drugs are excreted in human breast milk and because of the potential for adverse reactions in nursing infants, nursing should be discontinued when receiving megestrol acetate therapy.

HIV Infected Women

Although megestrol acetate has been used extensively in women for the treatment of endometrial and breast cancers, its use in HIV infected women has been limited. All 10 women in clinical trials reported breakthrough bleeding.

Drug Interactions

Possible interactions of megestrol acetate with concomitant medications have not been investigated.

Information for Patients

Patients should be advised to use MEGESTROL as directed and report any adverse reaction experiences to their physician. Women of childbearing potential should be advised to avoid becoming pregnant and should exercise adequate contraceptive control. If patients become pregnant while taking MEGESTROL, they should promptly notify their physician.

ADVERSE REACTIONS

Weight gain is a frequent side effect of megestrol acetate when it is used in patients with cancer of the breast or endometrium. This gain is associated with increased appetite. It is this effect which forms the basis for use of megestrol acetate in patients with anorexia, cachexia or weight loss. Weight gain is associated with an increase in fat and body cell mass.

Untoward reactions that have been reported to occur in patients receiving megestrol acetate include nausea, vomiting, edema and breakthrough uterine bleeding and occur in approximately 1% to 2% of patients. Gynecomastia and loss of hearing have also been reported. Dyspnea, heart failure, hypertension, hot flashes, mood changes, cushingoid facies, tumor flare (with or without hypercalcemia), hyperglycemia, alopecia, carpal tunnel syndrome and rash have also occurred.

Thromboembolic phenomenon including thrombophlebitis and pulmonary embolism (in some cases fatal) have also been reported.

Laboratory evidence of pituitary–adrenal axis abnormalities has been observed in patients treated with megestrol acetate. Although the significance of these laboratory findings has not been fully established, clinically apparent adrenal insufficiency has been reported to occur rarely in patients shortly after megestrol acetate was discontinued. Patients should be observed for clinical evidence of adrenocortical insufficiency when megestrol acetate is abruptly withdrawn.

In patients with advanced, non–endocrine–sensitive cancer who received doses of megestrol acetate up to 480 mg/day in a clinical trial for anorexia and weight loss, dyspnea, nausea, edema, pain, lethargy and diarrhea were observed commonly. Constipation and urinary frequency also have been reported in patients who received high doses of megestrol acetate in other clinical trials.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Usual safety measures as with the overdose of any medication should be instituted. However, no serious unexpected side effects have resulted from studies involving megestrol acetate administered in dosages as high as 1600 mg/day for 6 months or more. Megestrol acetate has not been tested for dialyzability; however, due to its low solubility, it is postulated that dialysis would not be an effective means of treating overdose.

DOSAGE AND ADMINISTRATION

For the following indications, at least two months of continuous treatment is considered an adequate period for determining the efficacy of MEGESTROL (megestrol acetate) tablets.

For palliative or adjunctive treatment of breast carcinoma: 160 mg or 125 mg/m^2 daily (40 mg q.i.d. or 160 mg q.d.).

For endometrial carcinoma: 80 - 320 mg or 62.5 - 250 mg/m^2 daily in divided doses (40 - 80 mg one to four times daily or one to two 160 mg tablets daily).

For palliative treatment of hormone responsive advanced (Stage D_2) carcinoma of the prostate: 120 mg (93.8 mg/m^2) as a single daily dose in combination with diethylstilbestrol tablet, 0.1 mg.

For anorexia, cachexia, or significant weight loss in patients with cancer: usual adult dose: 400 to 800 mg as a single daily dose.

PHARMACEUTICAL INFORMATION

Drug Substance

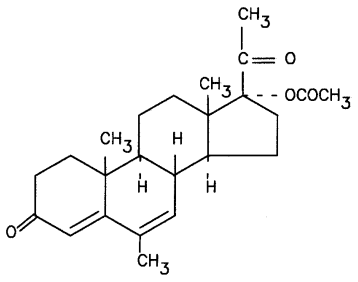
Brand Name: MEGESTROL

Common Name: Megestrol acetate

Chemical Names: 1) Pregna-4,6-diene-3, 20-dione, 17-(acetyloxy)-6-methyl;

2) 17-Hydroxy-6-methylpregna-4,6-diene-3, 20-dione acetate.

Structural Formula:



Molecular Formula: $C_{24}H_{32}O_4$

Molecular Weight: 384.52

Description: Megestrol acetate is a white to creamy–white, odourless, crystalline powder. Megestrol acetate is insoluble in water, sparingly soluble in alcohol, slightly soluble in ether and in fixed oils. It is soluble in acetone and very soluble in chloroform. Megestrol acetate is unstable under aqueous conditions at pH 7 or above. It has a melting point of 213 – 219°C.

Composition

MEGESTROL (Megestrol Acetate Tablets USP) 40 mg and 160 mg contain the following non–medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose, magnesium stearate and microcrystalline cellulose. MEGESTROL (Megestrol Acetate Tablets USP) 40 mg also contain Brilliant Blue FCF Lake 12% (dye).

Stability and Storage Recommendations

Store MEGESTROL (Megestrol Acetate Tablets USP) at room temperature (15-30°C) in well-closed containers.

AVAILABILITY OF DOSAGE FORMS

MEGESTROL (Megestrol Acetate Tablets USP) 40 mg: each light blue, round, flat–faced, bevelled–edged, scored tablet, engraved "40" on one side, contains 40 mg megestrol acetate. Available in bottles of 100 and 250, and unit dose packages of 100 tablets.

MEGESTROL (Megestrol Acetate Tablets USP) 160 mg: each white, oval, biconvex, scored tablet engraved "160" on one side, contains 160 mg megestrol acetate. Available in bottles of 100 and 250, and unit dose packages of 100 tablets.

PHARMACOLOGY

Animal Pharmacology

Besides its progestational effect, megestrol acetate also has antigonadotropic, antiuterotropic and antiandrogenic/antimyotropic actions. It has a slight but definite glucocorticoid activity and a very slight mineralocorticoid action. It is inactive as an estrogen, androgen or anabolic agent.

There were marginal or no significant effects in routine anticancer screening in mice and rats for mammary fibroadenoma or adenocarcinoma, methylcholanthrene carcinoma, acute leukemia and Dunning leukemia, and spontaneous uterine leiomyosarcoma. Malignant lymphoma in mice may have been stimulated.

Human Pharmacology - Pharmacokinetics and Bioavailability

Megestrol acetate tablets 40 mg, 160 mg regular and 160 mg micronized were administered to 24 healthy male volunteers (age 19-44 years) in a three–way crossover bioequivalence study, balanced for sequence, with a week between dose administrations. The 40 mg tablets were administered q.i.d. at 8:00, 12:00, 18:00 and 22:00 hours, while the 160 mg tablets were administered at 8:00 h. Plasma samples were collected up to 96 hours after administration and analyzed for megestrol acetate.

Table 1 presents a summary of the mean (SD) pharmacokinetic parameters. The rates of absorption were essentially identical for all three formulations. Based on AUC, the extent of absorption were essentially the same for all three formulations. Neither mean retention time (MRT) nor half–life were different between formulations, however there was a high degree of subject variability. C_{max} values were not comparable for all formulations. Relative to the 40 mg q.i.d. dose, the 160 mg regular and 160 mg micronized tablets had mean bioavailabilities of 97% and 118%, respectively.

Table 1			
Pharmacokinetic Parameter	40 mg q.i.d.	160 mg Regular	160 mg Micronized
C_{max} (ng/mL)	107.3 (30.2)	88.9 (36.8)	133.7 (35.4)
T_{max} (ng/mL)	2.5* (1.6)	2.8 (1.4)	2.8 (0.8)
AUC (ng.hr/mL)	2248.8 (811.3)	1979.7 (736.7)	2473.5 (530.7)
MRT (hr)	47.2 (35.4)	52.5 (35.9)	33.5 (8.9)
T_{half} (hr)	33.2 (30.9)	37.6 (27.1)	23.5 (8.0)
* After the initial dose			

Megestrol acetate tablets, 750 mg (3 x 250 mg) and oral suspension 750 mg (40 mg/mL) were administered once daily to 24 asymptomatic, HIV seropositive male patients in a two–period bioequivalence study. Each treatment was administered for 14 days with no washout period between treatments. Steady state plasma megestrol acetate concentrations were determined over a 24–hour period and pharmacokinetic parameters were determined non–compartmentally. When using the suspension as the reference dosage form, there was no significant difference in T_{max} and C_{max} plasma values for the tablet and suspension and the values fell within an 80 to 120% range, suggesting similar rates of bioavailability for the formulations. The mean AUC value for the tablet was 12% greater than for the suspension. Thus it would appear that no clinically–significant difference would be found between a dose of three 250 mg tablets and 750 mg of 40 mg/mL suspension, and they would be therapeutically interchangeable. Relative to the oral suspension, the 250 mg tablets had a mean bioavailability of 116%. The pharmacokinetic parameters are presented in Table 2.

Table 2		
Pharmacokinetic Parameter	750 mg Tablet (3 x 250 mg)	750 mg Oral Suspension (18.75 mL x 40 mg/mL)
C_{max} (ng/mL)	458.0 (183.0)	490.0 (238.0)
T_{max} (ng/mL)	3.0 (1.0 - 6.0)	3.0 (0.0 - 8.0)*
AUC (ng.hr/mL)	7650.0 (3780.0)	6779.0 (3048.0)
* Median value and range		

In a pharmacokinetic study in patients with AIDS, ten adult male cachectic patients (age 26 - 49 years) with an involuntary weight loss greater than 10% of baseline received daily oral doses of 800 mg of an oral

suspension containing 40 mg/mL of micronized megestrol acetate for 21 days. Plasma samples were taken just prior to dosing on days 19, 20 and 21 and at intervals for 48 hours after dosing on day 21. All plasma samples were analyzed for intact megestrol acetate.

A high degree of intra–patient variability in rate of absorption was observed. Table 3 provides a summary of the median pharmacokinetic parameters.

Table 3		
AUC_{0-24} (ng.hr/mL)	C_{max} (ng/mL)	T_{max} (hr)
7547.0 (1550.0 - 27090.0)	602.0 (77.0 - 1670.0)	5.0 (1.0 - 8.0)

TOXICOLOGY

Acute Toxicity

Megestrol acetate when given orally to mice is non–toxic at levels of 5 g/kg.

Subacute and Chronic Toxicity

Megestrol acetate given orally to rats for 3 months at doses of 1 mg/kg and 20 mg/kg had no effect on the growth of both males and females. Adrenal atrophy was seen in the females at the 20 mg/kg dose. Uterine sections showed endometrial hyperplasia, due to the progestational activity of megestrol acetate.

A trend towards increased frequency of respiratory infections, decreased lymphocyte counts and increased neutrophil counts was observed in a two–year chronic toxicity/carcinogenicity study of megestrol acetate conducted in rats.

Administration for up to 7 years of megestrol acetate to female dogs is associated with an increased incidence of both benign and malignant tumors of the breast. Comparable studies in monkeys for up to 10 years are not associated with an increased incidence of malignant tumors. The relationship of the dog tumors to humans is unknown but should be considered in assessing the benefit–to–risk ratio when prescribing megestrol acetate and in surveillance of patients on therapy.

Two long–term studies were performed on beagle dogs and monkeys. Groups of 20 female beagle dogs were given 0, 0.01, 0.10, or 0.25 mg/kg/day of megestrol acetate (0, 1, 10 or 25 times the anticipated human dose, on a mg/kg basis) or 0.25 mg/kg/day of chlormadinone acetate. Groups of 20 female rhesus monkeys were given 0, 0.01, 0.10 or 0.50 mg/kg/day (0, 1, 10 or 50 times the anticipated human dose, on a mg/kg basis) or 0.50 mg/kg/day of chlormadinone acetate. Up to the end of 7 years, 2 dogs at doses of 0.1 mg/kg/day and 5 dogs at 0.25 mg/kg/day exhibited mammary carcinoma with metastasis. Multiple mammary nodules were also seen in all dogs in these two dosage groups as well as one or two nodules in 3 of the 12 control animals. At the end of 5 years, one monkey at a dose of 0.01 mg/kg/day and one monkey at a dose of 0.10 mg/kg/day exhibited palpable nodules but were not malignant. Reduction in menses in the monkeys with near cessation of cyclic activity at 0.05 mg/kg/day, and a decreased evidence of estrus and mucoid vaginal discharges were noted in the beagle dogs.

At the end of the sixth year, elevations in erythrocyte sedimentation rate (ESR) were seen in dogs at the 0.1 and 0.25 mg/kg doses. Decreased hemoglobin (Hgb), hematocrit (Hct) and red blood cells (RBC) were seen in the latter group and scattered lowering of Hgb was observed in the former group. Serum cholesterol and blood sugar were elevated and serum calcium depressed in the 0.25 mg/kg/group. Serum cholesterol was elevated in the 0.1 mg/kg/group. Bilateral cataracts were observed in 1 of 6 dogs on the 0.25 mg/kg/dose. In addition to the changes in the breasts as previously described, necropsy findings in 3 of the 6 dogs at both doses included cachexia, discoloured lungs, enlarged livers, dark–green and viscous gallbladder contents, enlarged and discoloured kidneys, enlarged uteri and lymph nodes and cystic ovaries.

In monkeys at the end of 5 years, physical ophthalmoscopic examinations and clinical laboratory studies revealed no treatment–related effects. At the end of the 10–year study, there were no compound–related changes in mortality, physical appearance and behaviour, body weight gain, ophthalmology, hematology, urinalysis, terminal body weights and gross tissue findings.

Minor related findings include a dose–dependent decrease in menstrual activity and in mean uterine weights, as well as a depressed estrogenic activity in the mid– and high–dose groups (0.1, 0.5 mg/kg/day). Histopathologic examination revealed inhibition of ovulation, increased numbers of hyalinized ovarian atretic follicles, increased cervical glandular dilatation, and increased cervical mucoid secretion in the mid– and high–dose groups. Cyclic endometrial changes were evident for all monkeys, but no mammary hyperplastic or neoplastic changes were found.

Carcinogenesis

Data on carcinogenesis were obtained from studies conducted in dogs, monkeys and rats treated with megestrol acetate. No males were used in the dog and monkey studies. In female beagle dogs, megestrol acetate (0.01, 0.1 or 0.25 mg/kg/day) administered for up to 7 years induced both benign and malignant tumours of the breast. In female monkeys, no tumours were found following 10 years of treatment with 0.01, 0.1 or 0.5 mg/kg/day megestrol acetate. Pituitary tumors were observed in female rats treated with 3.9 or 10 mg/kg/day of megestrol acetate for 2 years. The relationship of these tumors in rats and dogs to humans is unknown but should be considered in assessing the risk–to–benefit ratio when prescribing megestrol acetate and in surveillance of patients on therapy.

Mutagenesis

No data on mutagenesis is currently available.

Impairment of Fertility

Perinatal/postnatal (segment III) toxicity studies were performed in rats at doses of 0.05 to 12.5 mg/kg. In these low–dose studies, the reproductive capability of male offspring of megestrol acetate–treated females was impaired. Similar results were obtained in dogs. Pregnant rats treated with megestrol acetate showed a reduction in fetal weight and number of live births, and terminization of male fetuses. No toxicity data are currently available on male reproduction (spermatogenesis).

Teratology

No adequate teratology information is available at clinically relevant doses.

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