

PRODUCT MONOGRAPH

MEGACE* OS

(megestrol acetate)

Oral Suspension USP, 40 mg/mL

Antianorexic / Anticachectic

Bristol-Myers Squibb Pharmaceutical Group
Division of Bristol-Myers Squibb Canada Inc.
Montreal, Canada.

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* TM auth. user
Bristol-Myers Squibb Canada Inc.

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PRODUCT MONOGRAPH

NAME OF DRUG

MEGACE* OS

(megestrol acetate)

Oral Suspension USP, 40 mg/mL

THERAPEUTIC CLASSIFICATION

Antianorexic / Anticachectic

ACTIONS AND CLINICAL PHARMACOLOGY

The precise mechanism of action by which megestrol acetate produces its antianorexic and anticachectic effects is 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 qid regimen, the oral absorption of MEGACE 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 qid regimen have not been established.

Plasma steady state pharmacokinetics of MEGACE OS (megestrol acetate) were evaluated in 10 adult cachectic male patients (age 26-49 years) with acquired immunodeficiency syndrome (AIDS) and an involuntary weight loss greater than 10% of baseline. Patients received single oral dose of 800 mg/day of megestrol acetate for 21 days. Plasma concentration data obtained on day 21 were evaluated for up to 48 hours past the last dose. A high degree of interpatient variability in rate and extent of absorption was

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

observed. Median peak plasma concentration (C_{max}) of megestrol acetate was 602 ng/mL (range 77 to 1670 ng/mL). Median area under the concentration versus time-curve (AUC) was 7547 ng·hr/mL (range 1550 to 27090 ng·hr/mL) and median T_{max} value was 5.0 hr (range 1 to 8 hours).

Steady state plasma pharmacokinetics of MEGACE OS were evaluated in 24 asymptomatic HIV seropositive male patients (age 21-40 years). Patients received single oral dose of 750 mg of megestrol acetate for 14 days. The mean plasma concentration (C_{max}) of megestrol acetate was 490 ng/mL (range 156-1169 ng/mL). The mean area under the concentration vs time curve (AUC) was 6779 hr·ng/mL (range 1826 to 14094 hr·ng/mL) and median T_{max} was 3.0 hours (range 0-8 hours).

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

There are no alterations in pharmacokinetic parameters when megestrol acetate (oral suspension) is administered with zidovudine or rifabutin.

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% (range 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.

INDICATIONS AND CLINICAL USES

MEGACE (megestrol acetate) Oral Suspension is indicated for the treatment of anorexia, cachexia, or an unexplained significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).

CONTRAINDICATIONS

MEGACE (megestrol acetate) Oral Suspension is contraindicated in those people who are sensitive to megestrol acetate or any ingredients in the dosage form. MEGACE 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. 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 1 000 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, however some of these drugs induce mild virilization of the external genitalia of the female fetus.

If the patient is exposed to MEGACE (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.

MEGACE OS is not intended for prophylactic use to avoid weight loss.

PRECAUTIONS

General

Therapy with MEGACE OS (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.

Although the glucocorticoid effects of MEGACE OS in HIV-infected individuals have not been evaluated, laboratory evidence of adrenal suppression has been observed rarely in patients shortly after discontinuation of MEGACE OS therapy. The significance of these findings has not been fully established. The possibility of adrenal suppression should be considered in all patients taking or withdrawing from chronic megestrol acetate therapy. Replacement stress doses of glucocorticoids may be indicated.

Effects of MEGACE OS on HIV viral replication have not been determined.

Use MEGACE/MEGACE OS 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 MEGACE continuously for prolonged periods should be observed closely for possible adrenal cortical suppression.

Pediatric Use

Safety and effectiveness in pediatric patients 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 MEGACE 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 MEGACE with concomitant medications have not been investigated.

Information for Patients

Patients should be advised to use MEGACE 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 MEGACE, 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 has been 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 MEGACE (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, pain, heart failure, hypertension, hot flashes, mood changes, cushingoid facies, tumor flare (with or without hypercalcemia), hyperglycemia, alopecia, carpal tunnel syndrome, diarrhea, lethargy and rash have also been reported.

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

Pituitary adrenal axis abnormalities including glucose intolerance, new onset diabetes, exacerbation of preexisting diabetes with decreased glucose tolerance and Cushing's syndrome have been reported with the use of megestrol acetate.

In clinical trials of megestrol acetate in patients with acquired immune deficiency syndrome, overall, there was no statistically significant difference between active and placebo treatment in patients reporting at least one adverse events. Events reported in $\geq 5\%$ of these study patients included diarrhea, impotence, rash, flatulence, asthenia and pain. Aside from impotence, all occurred more commonly in patients receiving placebo treatment.

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 MEGACE (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 with MEGACE OS (megestrol acetate oral suspension) is recommended.

Anorexia, cachexia, or significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS):

Usual adult dose: 400 to 800 mg as a single daily dose (10 to 20 mL/day). Two teaspoonfuls (10 mL) of oral suspension contain 400 mg of megestrol acetate.

Shake container well before use.

PHARMACEUTICAL INFORMATION

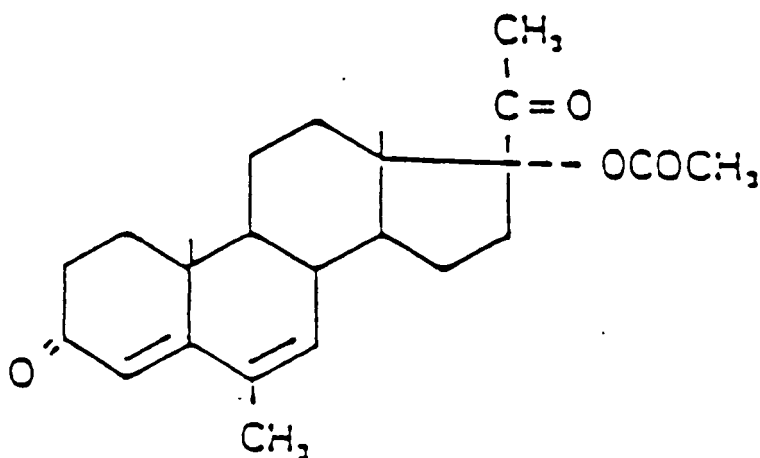
I. DRUG SUBSTANCE

Proper Name: Megestrol acetate

Chemical Name: 17-hydroxy-6-methylpregna-4, 6-diene-3, 20-dione acetate.

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

Structural Formula:



Molecular Weight: 384.5

Description: Megestrol acetate is a white to creamy-white, odorless, crystalline powder with a melting point of 213-219°C. It is insoluble in water; sparingly soluble in ethanol; and soluble in acetone and chloroform.

II. COMPOSITION

In addition to the active ingredient, megestrol acetate, each mL of oral suspension contains xanthan gum, polysorbate 80, anhydrous citric acid, sucrose, sodium benzoate, sodium citrate dihydrate, polyethylene glycol 1450, purified water and natural and artificial lemon-lime flavor.

III. STABILITY AND STORAGE RECOMMENDATIONS

Store oral suspension at room temperature (15-30°C). Protect from temperatures above 30°C.

IV. SPECIAL INSTRUCTIONS

Exposure or overdose at levels approaching recommended dosing levels could result in side effects described above (see WARNINGS and ADVERSE EVENTS). Women at risk of pregnancy should avoid such exposure.

AVAILABILITY OF DOSAGE FORMS

MEGACE (megestrol acetate) Oral Suspension is available as a lemon-lime flavored oral suspension containing 40 mg of micronized megestrol acetate per mL. Bottles of 240 mL.

PHARMACOLOGY

Animal Pharmacology

Besides its progestational effect, megestrol acetate also has antigonadotropic, antiuterotropic, and antiandrogenic/antimytropic 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, 750 mg (3 x 250 mg) and oral suspension 750 mg (40 mg/mL) was 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 tablet had a mean bioavailability of 116%. The pharmacokinetic parameters are presented in Table 1.

TABLE 1

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)
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* 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 2 provides a summary of the median pharmacokinetic parameters.

TABLE 2

AUC₀₋₂₄ (ng·hr/L)	C_{max} (ng/mL)	T_{max} (ng/mL)
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 toward 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 tumours. 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 behavior, 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 tumors of the breast. In female monkeys, no tumors 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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