



Apo-Megestrol

Megestrol acetate 160mg tablets USP

Presentation

APO-MEGESTROL 160 mg: white, oval, biconvex, scored tablets, engraved "APO 160" on one side, containing 160mg megestrol acetate.

Uses

Actions

The precise mechanism by which megestrol acetate produces its antineoplastic effects against endometrial carcinoma is unknown, but an antiluteinizing effect mediated via the pituitary has been postulated. There is also evidence to suggest a local effect as a result of the marked changes brought about by the direct instillation of progestational agents into the endometrial cavity. Likewise, the antineoplastic action for megestrol acetate on carcinoma of the breast is unclear.

Megestrol acetate has many of the properties of naturally occurring progesterone. Although its dose-dependent mode of action is identical to that of medroxyprogesterone acetate (MPA), its progestational potency is greater than MPA, with megestrol acetate 160 to 200mg p.o. equal to 1000 to 1500mg of MPA. The progestational potency of megestrol acetate is also greater than that of norethindrone and norethynodrel, but slightly less than that of chlormadinone acetate, and significantly less than that of norgestrel.

Megestrol acetate possesses significant antiestrogenic activity and has displayed antigonadotropic effects and slight but definite glucocorticoid activity. It has no estrogenic and little, if any, mineralocorticoid activity. In conventional doses it has not exhibited any anabolic or androgenic properties.

Megestrol acetate acts as an appetite enhancing agent in cachexia. The precise mechanism by which megestrol acetate produces its antianorexia and anticachexia effects is unknown at the present time.

The efficacy of megestrol acetate in anorexia and cachexia has been established in placebo-controlled trials where patients have received up to 800 mg/day of megestrol acetate. A dose response model was fitted to the maximum weight gain, which was shown to be statistically significant. The improvement in appetite was found to be statistically significant. Patients tolerated the drug well and no statistically significant differences were seen between treatment groups with regard to laboratory toxicities, new opportunistic infections, lymphocyte counts, T4 counts, T8 counts, or skin reactivity tests.

Pharmacokinetics

Absorption:

In humans, megestrol acetate is rapidly absorbed following oral administration. Peak plasma levels are reached at about two hours, and the half-life is four hours. After a single oral administration of 60mg of megestrol acetate to healthy females, the plasma level reached a mean maximum of 43ng/ml after one to four hours; after 24 hours it was still detectable (9.6 to 29ng/ml) and after seven days it was in the range of 0.7 to 3.2ng/ml. There are several methods used to estimate megestrol acetate plasma levels, including mass fragmentography and radioimmunoassay. The plasma levels are dependent not only on the method used, but also on intestinal and hepatic inactivation of the drug, which may be affected by factors such as intestinal tract motility, intestinal bacteria, antibiotic administration, body weight, diet and liver function.

A clinical study in which megestrol acetate was administered in a 160mg single daily dose to metastatic breast cancer patients showed no major differences in responses to single daily dose megestrol acetate as compared to responses expected with a multiple daily dose regimen.

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Distribution:

Similar peak plasma concentrations (90-110ng/mL) occur after the administration of one 160mg tablet or four 40mg tablets given over 24 hours. The extent of absorption (AUC) was also not different between the two dosage forms. The plasma half-life was 33 to 38 hours.

Metabolism:

The metabolic degradation of megestrol acetate was studied in five women; four received doses of 60 to 91mg and one received a dose of only 4mg. The compound was radioactively labelled on the 6-methyl group.

The biological half-life of the compound was three and a half days among the women who received the higher dose, but was less than one day in the woman taking the lower dose. Three major metabolites, excreted as glucuronide conjugates, were identified.

The identification of these metabolites suggests the occurrence of hydroxylation at the C-2 position, the 6-methyl position, or both.

Other metabolites of megestrol acetate have been noted; although unconjugated steroids were quantitatively as significant as those excreted as glucuronides in the preceding study, their higher polarity and impurity prevented identification. The three identified metabolites accounted for only 5% to 8% of the administered dose.

Excretion:

The major route of elimination of megestrol acetate in humans is the urine. When radioactively labelled megestrol acetate was administered orally to humans in doses of four to 50mg, the urinary excretion within ten days ranged from 56.5% to 78.4% (mean 66.4%) and faecal excretion ranged from 7.7% to 30.3% (mean 19.8%). The total recovered radioactivity varied between 83.1% and 94.7% (mean 86.2%). These values are in general agreement with those obtained with megestrol acetate in rabbits and with progesterone in humans.

Respiratory excretion as $^{14}\text{CO}_2$ and fat storage may have accounted for at least part of the radioactivity not found in the urine or faeces.

Indications

Apo-Megestrol is indicated for the palliative treatment of advanced carcinoma of the breast or endometrium (i.e. recurrent, inoperable or metastatic diseases). It should not be used in lieu of currently accepted procedures such as surgery, radiation or chemotherapy.

Apo-Megestrol is indicated for the treatment of anorexia, cachexia, or a significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).

Dosage and Administration

Breast Cancer:

160mg/day (160mg taken once daily).

At least two months of continuous treatment is considered an adequate period for determining the efficacy of Apo-Megestrol

Contraindications

Apo-Megestrol is contraindicated as a diagnostic test for pregnancy.

Apo-Megestrol is contraindicated in patients with a history of hypersensitivity to megestrol acetate or any component of the formulation.

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Warnings and Precautions

Use in Pregnancy

Category D

Progestational agents have been used beginning with 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 foetus 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 fertilised defective ova may cause a delay in spontaneous abortion. Therefore, the use of such drugs during the first four months of pregnancy is not recommended.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital heart defects and limb reduction defects. One study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted threatened abortion). Some of these exposures were very short and involved only a few days' treatment. The data suggest that the risk of limb reduction defects in exposed foetuses is somewhat less than 1 in 1,000.

If the patient is exposed to megestrol acetate during the first four months of pregnancy, or if she becomes pregnant while taking this medicine, she should be apprised of the potential risks to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant. Administration of megestrol acetate for up to 7 years to female beagle dogs is associated with increased incidence of both benign and malignant tumours of the breast. Comparable studies in rats and ongoing studies in monkeys are not associated with any increased incidence of tumours. The relationship of the dog tumours to humans is unknown but should be considered in assessing the benefit-to-risk ratio when prescribing Apo-Megestrol and in surveillance of patients on therapy.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female foetuses. 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 foetuses, but insofar as some of these drugs induce mild virilization of the external genitalia of the female foetus, and because of the increased association of hypospadias in the male foetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy. Fertility and reproduction studies with high doses of megestrol acetate have shown a reversible feminising effect on some male rat foetuses.

The use of Apo-Megestrol in other types of neoplastic disease is not recommended.

There are no specific precautions identified for the use of Megestrol acetate when used in humans as recommended. Close, customary surveillance is indicated for any patient being treated for recurrent or metastatic cancer. Use with caution in patients with a history of thrombophlebitis.

Use in Lactation

Because of the potential for adverse effects on the newborn, nursing should be discontinued during treatment with Apo-Megestrol.

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Use in Children

Safety and effectiveness in children have not been established.

Adverse Effects

Weight Gain:

Weight gain is a frequent side effect of megestrol acetate. This gain has been associated with increased appetite. Weight gain is caused by an increase in fat and body cell mass, 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:

Nausea and vomiting, flatulence, abdominal pain, headache, dry mouth, dyspepsia, oedema, breakthrough bleeding, dyspnoea, cough, heart failure, hypertension, hot flushes, mood changes, cushingoid facies, paresthesia, asthenia, insulin-dependent diabetes, elevation of liver enzymes, albuminuria, constipation, decreased libido, impotence, tumour flare (with or without hypercalcaemia), hyperglycaemia, alopecia, insomnia, carpal tunnel syndrome, diarrhoea, lethargy, and rash have occurred rarely.

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 event. Events reported in $\geq 5\%$ of these study patients included diarrhoea, impotence, rash, flatulence, asthenia and pain. Aside from impotence, all occurred more commonly in patients receiving placebo treatment.

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. Clinically apparent adrenal insufficiency has been reported rarely in patients shortly after megestrol acetate was discontinued. 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.

Interactions

None known.

Overdosage

No serious side effects have resulted from studies involving megestrol acetate administered in dosages as high as 1600mg/day for 6 months or more. No acute toxicological effects have been recognised in these studies. Oral administration of large single doses of megestrol acetate (5g/kg) did not produce toxic effects in mice.

Due to low solubility of megestrol acetate it is unlikely that dialysis would be an effective means of treating overdosage.

Pharmaceutical Precautions

Shelf Life for 160mg tablets from date of manufacture is 36 months.

Store at or below 25°C. Protect from heat, light and moisture. Keep container tightly closed.



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Medicine Classification

Prescription Only Medicine.

Package Quantities

APO-MEGESTROL 160mg tablets are available in bottles of 30.

Further Information

Tablets contain Lactose Monohydrate

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