MEGESTROL ACETATE TABLETS, USP
Rx only
DESCRIPTION
Megestrol acetate is a synthetic, antiprogestational and progestational drug. Megestrol acetate is a white, crystalline solid chemically designated as 17α-[(2Z)-4-cyclohexene-6,6-dimethyl-4,6-dione-3,20-dinitro-1] lactone. Solubility is 37°C in water (2 mg per mL), soluble in 24 mg per mL of its molecular weight is 364.51. The molecular formula is C28H24O4 and the structural formula is represented as follows:

CLINICAL PHARMACOLOGY
While the precise mechanism by which megestrol produces its antineoplastic effects against endometrial carcinoma is unknown, it is possible that effects on pituitary gland function and resultant decrease in estrogen secretion may be factors. There is evidence to suggest a local effect as a result of the marked changes brought about by the direct indifferent effect of megestrol acetate on the normal progestational cells. The primary antineoplastic action of megestrol acetate on the breast is effected by modifying the uterine-like activity of the endometrial and breast epithelial cells, thus preventing the formation of tumors in the cellular layer. The secondary action of the hormone is the prevention of the formation of cancerous tumors. In contrast, the hormone is also capable of modifying and abolishing the stimulatory effects of estrogen on these cells. It has been suggested that progesterone may inhibit in one of two ways, by interfering with either the stability, availability, or turnover of the estrogen receptor complex in its interaction with genes or by cancelling the effect of the progesterone receptor complex, by interacting directly with the genome to form a specific antineoplastic gene.

There are several analytical methods used to estimate megestrol acetate plasma levels, includes mass fragmentography, gas chromatography (GC), high pressure liquid chromatography (HPLC), and radioimmunoassay. The plasma levels by HPLC assay or radioimmunoassay methods are about one-sixth those obtained by the GC method. 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, interstitial bacteria, antibiotics administered, body weight, diet, and liver function.

Metabolites account for only 5 to 8% of the administered dose and are not associated with any adverse effect. The main metabolite is 20α-hydroxy megestrol acetate, which is eliminated in the urine. After radiolabeled megestrol acetate was administered to humans in doses of 4 to 90 mg, the urinary excretion within 10 days ranged from 56.5% to 78.4% (mean 66.4%) and fecal excretion ranged from 7.7% to 30.3% (mean 19.8%). The total recovery varied between 83.1% and 94.7% (mean 86.2%). Respiratory excretion as labeled carbon dioxide and fat storage may have accounted for at least part of the radioactivity not found in the urine and feces.

In normal male volunteers (n=23) 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. Plasma levels were assayed by a high pressure liquid chromatographic (HPLC) procedure. Peak drug levels for the first 40 mg dose ranged from 10 to 52 ng/mL (mean 22.9 ng/mL) and the mean to peak concentrations ranged from 1.5 to 3.9 (mean 3.5) ng/mL and from 1 to 30 hours (mean 12 hours) and from 4 to 20 hours (mean 54.2 hours). The steady state plasma concentrations for a 40 mg q.i.d. regimen have not been established.

INDICATIONS AND USAGE
Megestrol acetate tablets are indicated for the palliative treatment of advanced carcinoma of the breast or endometrium (i.e., recurrent, inoperable, or metastatic disease). It should not be used in lieu of currently accepted procedures such as surgery, radiation, or chemotherapy.