MEGESTROL ACETATE TABLETS, USP
Rx only
DESCRIPTION
Megestrol acetate is a synthetic, antineoplastic and progestational drug. It is a white, crystalline solid chemically designated as 17(alpha)-(acetyloxy)-6-methylpregna-4,6-diene-3,20-dione. Solubility at 37°C in water is 2 mcg per mL, solubility in plasma is 24 mcg per mL. Its molecular weight is 384.1. The molecular formula is C_{22}H_{22}O_{4} and the structure formula is represented as follows:

CLINICAL PHARMACOLOGY
While the precise mechanism by which megestrol produces its antineoplastic effects against endometrial carcinoma is unknown at the present time, inhibition of plurihormonogenesis production and resultant decrease in estrogen secretion may be factors. There is evidence to suggest a toxic effect as a result of the marked changes brought about by the direct action of megestrol acetate on estrogenic target tissues. The antineoplastic action of megestrol acetate on the breast is by modifying the action of other steroid hormones and by exerting a direct cytostatic effect on tumor cells. In malignant cancer, hormone receptors may be found in some tissues but not others. The receptor mechanism is a cyclic process whereby estrogen enters the cell, forms a complex with cytoplasmic receptor and is transported into the cell nucleus. There it induces gene transcription and leads to the alteration of normal cell functions. Pharmacokinetic doses of megestrol acetate not only decrease the number of hormone-dependent human breast cancer cells but also are capable of modifying and abolishing the stimulating effects of estrogen on these cells. It has been suggested that progestins may inhibit in one of two ways, by interfering with the stability, availability, or function of estrogen receptors, or by decreasing estrogen binding with conformational changes of the progestin receptor complex, thereby interacting directly with the genome to turn off specific estrogen-responsive genes.

There are several analytical methods used to estimate megestrol acetate plasma levels, including mass fragmentography, gas chromatography (GC), high pressure liquid chromatography (HPLC), and radioimmunoassay. The plasma levels by HPLC assay or radioimmunoassay method 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 metabolism of the drug, which may be affected by factors such as intestinal blood flow, hepatic and intestinal blood flow, dialyzability; however, due to its low solubility it is postulated that this is not a major factor. Administration of large, single doses of megestrol acetate did not produce toxic effects in mice. Megestrol acetate has not been tested for dailysafety; however, due to its low solubility it is postulated that this would not be an effective means of treating overdose.

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

CONTRAINDICATIONS
History of hypersensitivity to megestrol acetate or any component of the formulation.

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 in some male rats and females. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (revealing) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

The use of megestrol in other types of nongynecologic disease is not recommended. (See also PRECAUTIONS; Carcinogenesis, Mutagenesis, Impairment of Fertility section.)

The glucocorticoid activity of megestrol acetate tablets has not been fully evaluated. Clinical cases of new onset diabetes mellitus and hypoglycemia due to low doses of megestrol acetate have been described in patients with no previous history of diabetes. In addition, clinical cases of adrenal insufficiency have been observed in patients receiving or being withdrawn from chronic megestrol acetate therapy in the stressed and non-stressed state. Furthermore, adrenocorticosterone (ACTH) stimulation testing has revealed the frequent occurrence of asymptomatic pituitary-adrenal suppression in patients treated with chronic megestrol acetate therapy. Therefore, the possibility of adrenal insufficiency should be considered in any patient receiving or being withdrawn from chronic megestrol acetate therapy who presents with symptoms and/or signs suggestive of adrenocortical insufficiency (e.g., hypotension, nausea, vomiting, diarrhea, weakness, or weakness) in either the stressed or non-stressed state. In cases of paucity of adrenal replacement or stress test results of a rapidly acting glucocorticoid are strongly recommended in such patients. Failure to recognize inhibition of the hypothalamic-pituitary-adrenal axis may result in death. Finally, in patients who are receiving or being withdrawn from chronic megestrol acetate therapy, consideration should be given to the use of empiric therapy with stress doses of a glucocorticoid in the event of conditions of stress or serious intercurrent illness (e.g., surgery, infection).

PRECAUTIONS
General
Close surveillance is indicated for any patient treated for recurrent or metastatic cancer. Use with caution in patients with a history of thromboembolic disease.

Use in Diabetes
Exacerbation of pre-existing diabetes with increased insulin requirements has been reported in association with the use of megestrol.

Information for the Patients
Patients using megestrol acetate should receive the following instructions:
1. This medication is to be used as directed by the physician.
2. Report any adverse reaction experiences while taking this medication.

Laboratory Tests
Blood malignancies in which estrogen and/or progesterone receptors are positive are more likely to respond to megestrol. 
Carcinogenesis, Mutagenesis, Impairment of Fertility
Administration of megestrol acetate to female dogs for up to 7 years is associated with an increased incidence of both benign and malignant tumors of the breast. Comparable studies in rats and studies in monkeys are not associated with an increased incidence of tumors. The relationship of the dog tumors to humans is unknown but should be considered in assessing the benefits/burden ratio of megestrol acetate in patients with breast cancer and in surveillance of patients on therapy. (See WARNINGS section.)

Pregnancy
Pregnancy Category D (See WARNINGS section.)

Nursing Mothers
Because of the potential for adverse effects on the newborn, nursing should be discontinued if megestrol is required for treatment of cancer.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Insufficient data from clinical studies of megestrol acetate tablets are available for patients 85 years of age and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Megestrol acetate is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. 

ADVERSE REACTIONS
Weight Gain
Weight gain is a frequent side effect of megestrol. 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.

Glucocorticoid Effects
(See WARNINGS section.)

Other Adverse Reactions
Heart failure, nausea and vomiting, edema, breakthrough menstrual bleeding, dyspnea, tumor flare (with or without hypercalcemia), hyperglycemia, glucose intolerance, alopecia, hypertension, carpal tunnel syndrome, mood changes, hot flashes, malaise, alteration in weight, sweating and rash.

OVERDOSAGE
No serious unexpected side effects have resulted from studies involving megestrol acetate administered in dosages as high as 1600 mg/day. Oral administration of large, single doses of megestrol acetate (5 g/kg) did not produce toxic effects in mice. Megestrol acetate has not been tested for dailysafety; however, due to its low solubility it is postulated that this would not be an effective means of treating overdose.

DOSE AND ADMINISTRATION
Breast cancer: 160 mg/day (40 mg q.i.d.)
Endometrial carcinoma: 40 to 320 mg/day in divided doses.
At least 2 months of continuous treatment is considered adequate for determining the efficacy of megestrol acetate.

HOW SUPPLIED
Megestrol acetate tablets, 20 mg, are white, round, flat-faced, bisected, debossed with “Par 289” on one side. They are supplied in bottles of 100’s (NDC #49884-289-01). Megestrol acetate tablets, 40 mg, white, round, flat-faced, bisected, debossed with “Par 290” on one side. They are supplied in bottles of 100’s (NDC #49884-290-01), 250’s (NDC #49884-290-04) and 500’s (NDC #49884-290-05).

STORAGE
Store at 25°C (77°F); excursions are permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]. Protect from temperatures above 100°F.

SPECIAL HANDLING
Health Hazard Data
There is no threshold limit value established by OSHA, NIOSH, or ACGIH.

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

Manufactured by:
PARI PHARMACEUTICAL
Chesapeake Ridge, NY 10077

Revised: 04/16
OS289-01-11-12