MEGESTROL ACETATE ORAL SUSPENSION, USP

DESCRIPTION

Megestrol Acetate Oral Suspension, USP contains megestrol acetate, a synthetic derivative of the naturally occurring steroid hormone, progesterone. Megestrol acetate is a white, crystalline solid chemically designated as 3-17-hydroxy-6-methylene-4,9,11,13,17-penta-oladecynoic acid. Solubility at 37°C in water is 2 mg per mL, and solubility in plasma is 24 mg per mL. Its molecular weight is 384.52.

The chemical formula is C₂₄H₃₂O₄ and the molecular formula is H₂₅H₁₆O₄.

Megestrol acetate oral suspension is supplied as an oral suspension containing 40 mg of microcrystallized megestrol acetate per mL.

Megestrol acetate oral suspension contains the following inactive ingredients: alcohol (max 0.06% v/v from flavor), artificial flavor, citric acid monohydrate, dextrose, sodium citrate, sodium benzoate, sorbitol, sodium hydroxide, sucrose, and xanthan gum.

Megestrol acetate oral suspension, 40 mg/mL complies with USP Dissolution Test 2.

Megestrol acetate oral suspension contains the following inactive ingredients: alcohol (max 0.06% v/v from flavor), artificial flavor, citric acid monohydrate, dextrose, sodium citrate, sodium benzoate, sorbitol, sodium hydroxide, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

Several investigators have reported on the appetite enhancing property of megestrol acetate and its possible use in cachexia. The precise mechanism by which megestrol acetate produces effects in anorexia and cachexia is unknown at the present time.

There are several analytical methods used to estimate megestrol acetate plasma concentrations, including gas chromatography/mass fragmentography (GC-MF), high pressure liquid chromatography (HPLC) and radioimmunoassay (RIA). The GC-MF and HPLC methods are specific for megestrol acetate and the predispersed column in the GC-MF method allows for plasma concentrations to be measured that are higher than the GC-MF and HPLC methods. Plasma concentrations 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, antibiotics administered, body weight, diet and liver function.

The effect of food on the bioavailability of megestrol acetate oral suspension has not been evaluated.

The chemical formula is C₂₄H₃₂O₄ and the structural formula is represented as follows:

\[
\text{C}_2\text{H}_4\text{O}
\]

The molecular weight is 384.52.

MEGESTROL ACETATE ORAL SUSPENSION, USP contains megestrol acetate, a synthetic derivative of the naturally occurring steroid hormone, progesterone. Megestrol Acetate, mg/day

Baseline to Time of Maximum

% Patients With Improved Appetite:

Fat Body Mass (lb.)

Mean Changes in Body Composition

Baseline to 12 Weeks

Mean Change in Weight (lb.)

Evaluable Patients

Mean Change in Weight (lb.)

Baseline to 12 Weeks

Mean Changes in Body Composition

TRIAL 1

Study Accrual Dates

TRIAL 2

Study Accrual Dates

TRIAL 1

Study Accrual Dates

TRIAL 2

Study Accrual Dates

Baseline to Time of Maximum

Mean Weight Change

Placebo

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There were no statistically significant differences between treatment groups in mean caloric change or in daily weight measurements over a 12 week period or had one post baseline weight measurement but dropped out for therapeutic failure. The percent of patients gaining five or more pounds at last evaluation was 44.0% in the placebo group, 66.4% in the 400 mg group, 67.5% in the 400 mg group, and 72.1% in the 800 mg group.

In both trials, patients tolerated the drug well and no statistically significant differences were seen between the treatment groups with regard to laboratory abnormalities, new opportunistic infections, lymphocyte counts, CD4+ cells, or skin reactivity tests (see ADVERSE REACTIONS).

The following figures are the results of mean weight changes for patients evaluable for efficacy in trials 1 and 2.
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).

### INDICATIONS AND USAGE

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).

Megestrol acetate oral suspension is available as a milky white, lemon-lime flavored oral suspension containing 40 mg of micronized megestrol acetate per mL. The recommended adult initial dosage of Megestrol Acetate Oral Suspension, USP is 800 mg/day (20 mL/day). No serious unexpected side effects have resulted from studies involving megestrol acetate oral suspension administrated in doses as high as 12,000 mg/day. In premarketing experience, limited reports of overdose have been received. Signs and symptoms of overdose depend on the context of overdose, include nausea, vomiting, diarrhea, urinary retention, confusion, hyperglycemia, hypoglycemia, and ECG changes. No antidote for overdose with megestrol acetate oral suspension is known. In case of overdose, supportive and symptomatic therapy should be undertaken. Treatment should be directed toward correcting fluid and electrolyte imbalance, and consideration of treatment for seizures, hypotension, and respiratory depression as appropriate in the context of overdose. If seizures occur, management should include the use of anticonvulsant therapy. If hypotension occurs, fluid and electrolyte replacement should be administered. If respiratory depression occurs, oxygen and a ventilator should be administered as needed. Hemodialysis may be effective in removing megestrol acetate from the plasma of patients who are unresponsive to usual supportive measures.

### CONTRAINDICATIONS

- Megestrol acetate oral suspension is contraindicated in women who are pregnant or nursing. Megestrol acetate oral suspension is contraindicated in women who have had a hypersensitivity reaction to megestrol acetate oral suspension or any of its inactive ingredients.
- Megestrol acetate oral suspension is contraindicated in women who have a history of hypersensitivity to megestrol acetate or any component of the formulation. Known or suspected pregnancy.

*In the context of overdose, include nausea, vomiting, diarrhea, urinary retention, confusion, hyperglycemia, hypoglycemia, and ECG changes. No antidote for overdose with megestrol acetate oral suspension is known. In case of overdose, supportive and symptomatic therapy should be undertaken. Treatment should be directed toward correcting fluid and electrolyte imbalance, and consideration of treatment for seizures, hypotension, and respiratory depression as appropriate in the context of overdose. If seizures occur, management should include the use of anticonvulsant therapy. If hypotension occurs, fluid and electrolyte replacement should be administered. If respiratory depression occurs, oxygen and a ventilator should be administered as needed. Hemodialysis may be effective in removing megestrol acetate from the plasma of patients who are unresponsive to usual supportive measures.*

### WARNINGS

- Increases in hepatic transaminase activities have been observed in patients receiving megestrol acetate therapy. Megestrol acetate oral suspension should be used with caution in patients with impaired renal function. Megestrol acetate oral suspension should not be used to avoid weight loss. (See also PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility.) Carcinogenesis, Mutagenesis, Impairment of Fertility: Clinical studies of megestrol acetate oral suspension have not been performed in rats. Clinical cases of new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and overt Cushings Syndrome have been reported in association with the clinical use of megestrol acetate. In addition, clinical signs of hyperadrenocorticism have been observed in patients receiving or being withdrawn from chronic megestrol acetate therapy. Failure to recognize the hypoadrenocortical/adrenal-adrenal syndrome may result in death. Failure to recognize the hypoadrenocortical/adrenal-adrenal syndrome may result in death.

Patient Counseling:

- The patient should be apprised of the potential for hypoglycemia/insulinoma and for the symptoms associated with hypovitaminosis, e.g., nausea, vomiting, diarrhea. The patient should be advised to report the development of symptoms suggestive of hypoglycemia (e.g., weakness, dizziness, fatigue, irritability, sweating, chills, tremors, headache, drowsiness) to their physician, who will determine the need for a dose adjustment.

Antibiotics and/or nonsteroidal anti-inflammatory drugs, or their new formulations may cause an increase in hepatic transaminase activities. Megestrol acetate oral suspension should be used with caution in patients receiving concomitant therapy with these agents. If laboratory evidence of clinically significant hepatic transaminase increase occurs, the concomitant drug should be discontinued.

The recommended adult initial dosage of Megestrol Acetate Oral Suspension, USP is 800 mg/day (20 mL/day). The dose may be adjusted up or down based on benefit and tolerance. Megestrol acetate may cause fatal harm when administered to a pregnant woman. For animal data on fetal effects, see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility.

### ADVERSE REACTIONS

#### Adverse Events

**Clinical Adverse Events:** Adverse events which occurred in at least 1% of patients in any of the two clinical efficacy trials and the one that are listed below by treatment group. All patients (n=117) had at least one post baseline visit during the 12 study weeks. These adverse events should be considered by the physician when prescribing megestrol acetate oral suspension.

### PRECAUTIONS

- Megestrol acetate oral suspension contains a progesterone derivative, which may induce vaginal bleeding in women. Women at risk of pregnancy should avoid megestrol acetate oral suspension.
- Megestrol acetate oral suspension is not intended for prophylactic use to avoid weight loss. Megestrol acetate acetate for 2 years. The relationship of these tumors in rats and dogs to humans is unknown but should be considered.

### DOSAGE AND ADMINISTRATION

- The recommended adult initial dosage of Megestrol Acetate Oral Suspension, USP is 800 mg/day (20 mL/day). All adverse events occurring in at least 1% of patients in the two clinical efficacy trials with at least one follow-up visit after the first 12 weeks of the study are listed in Table 1. No adverse events occurring in less than 1% are included. There were no significant differences between incidence of these events in patients treated with megesterol acetate and placebo treated with placebo.

### OVERDOSE

No specific treatment has been reported for patients involving megestrol acetate oral suspension administrated in doses as high as 12,000 mg/day. In premarketing experience, limited reports of overdose have been received. Signs and symptoms of overdose depend on the context of overdose include nausea, vomiting, diarrhea, urinary retention, confusion, hyperglycemia, hypoglycemia, and ECG changes. No antidote for overdose with megestrol acetate oral suspension is known. In case of overdose, supportive and symptomatic therapy should be undertaken. Treatment should be directed toward correcting fluid and electrolyte imbalance, and consideration of treatment for seizures, hypotension, and respiratory depression as appropriate in the context of overdose. If seizures occur, management should include the use of anticonvulsant therapy. If hypotension occurs, fluid and electrolyte replacement should be administered. If respiratory depression occurs, oxygen and a ventilator should be administered as needed. Hemodialysis may be effective in removing megestrol acetate from the plasma of patients who are unresponsive to usual supportive measures.

**HOW SUPPLIED:**

Megestrol Acetate Oral Suspension, USP is available in 20 mL ampules and 800 mg/mL oral suspension. NDC: 49884-007-06. Bottles of 240 mL (505±10 mL). For intravenous administration.

Store the oral solution between 20° to 25°C (68° to 77°F). [See USP]. Dispense in a tight container. Protect from light.

**SPECIAL HANDLING:**

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

**Manufactured by:**

PAR PHARMACEUTICALS
Chesterfield, NC 28720

**Statistical Analysis:**

- Randomized, double-blind, placebo-controlled, parallel group design with treatment lasting at least 12 weeks. No significant differences between incidence of these events in patients treated with megestrol acetate and placebo treated with placebo.

- The recommended adult initial dosage of Megestrol Acetate Oral Suspension, USP is 800 mg/day (20 mL/day).

- In clinical trials evaluating different dose schedules, daily doses of 400 and 800 mg/day were found to be clinically effective.

- The recommended adult initial dosage of Megestrol Acetate Oral Suspension, USP is 800 mg/day (20 mL/day). MEGESTROL ACETATE ORAL SUSPENSION, USP for oral use only. MEGESTROL ACETATE ORAL SUSPENSION, USP contains no lactose, starch, or other excipients which may cause an allergic reaction in patients with a history of sensitivity to these substances.

- For Internal Use ONLY

- **NOTES:**

- **COMPANY NAME AND ADDRESS:**

- **NDC:**

- **MANUFACTURER:**

- **Website:**

- **Patient Package Insert:**

- **MFG:**

- **DISTRIBUTOR:**

- **LABELING:**

- **LABEL: CEI:**

- **Revised:**

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