MEZEST
Megestrol Acetate USP

COMPOSITION
Mezest 40 Tablet: Each film coated tablet contains Megestrol Acetate USP 40 mg.

Mezest 160 Tablet: Each film coated tablet contains Megestrol Acetate USP 160 mg.

PHARMACOLOGICAL INFORMATION
Megestrol Acetate is a synthetic, antineoplastic and progestational drug.

Mechanism of Action
The precise mechanism of action by which Megestrol Acetate produces its antineoplastic effects is unknown at present. It exerts a direct cytotoxic effect on human breast cancer cells and capable of modifying and abolishing the stimulatory effects of estrogen on breast cancer cell lines. Megestrol Acetate weight gain effect is related to its appetite-stimulant or metabolic effects rather than its glucocorticoid-like effects or the production of edema. It has also been suggested that Megestrol may alter metabolic pathyways via interferences with the production or action of mediators such as cachectin, a hormone that inhibits adipocyte lipogenic enzymes.

Pharmacodynamics
Mezest (Megestrol Acetate) possesses pharmacological properties similar to those of natural progesterone. Its progestational activity is slightly greater than that of Medroxyprogesterone Acetate, Norethindrone, Norethindrone Acetate and Norethynodrel; slightly less than that of chlormadinone Acetate and substantially less than that of Norgestrel.

Megestrol Acetate is a potent progestogen that exerts significant anti-oestrogenic effects. It has no androgenic or oestrogenic properties. It has anti-gonadotropic, anti-uterotropic and anti-androgenic/anti-myotropic actions. It has a slight but significant glucocorticoid effect and a very slight mineralocorticoid effect.

Pharmacokinetics
Absorption
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 60 mg of Megestrol Acetate to healthy females, the plasma level reached a mean maximum of 43 ng/ml after one to four hours; after 24 hours it was still detectable (9.6 to 29 ng/ml) and after seven days it was in the range of 0.7 to 3.2 ng/ml

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

Metabolism
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.

Elimination
Plasma half-life is 4-5 hours. The major route of elimination of Megestrol Acetate in humans is the urine.

INDICATIONS
Mezest 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.

Mezest 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
160 mg/day (160 mg taken once daily).
At least two months of continuous treatment is considered an adequate period for determining the efficacy of Mezest.
Best results are obtained in previously untreated receptor-positive cases that are more than five years post-menopausal (approximately 40% response rate). In patients with less favourable characteristics the response rate could be 15% or less.

Endometrial Carinoma
40 - 320 mg/day in divided doses (40 - 80 mg one to four times daily or one to two 160 mg tablets daily).

Cachexia
400 - 800 mg/day

Use in Children
Safety and effectiveness in children have not been established.

Use in the elderly
Insufficient data from clinical studies of Megestrol Acetate are available for patients 65 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 and 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.

Maximum Tolerated Daily Dose
Breast Cancer
160 mg/day
Endometrial Carinoma
320 mg/day
Cachexia
800 mg/day

Contraindications
Mezest is contraindicated as a diagnostic test for pregnancy. Mezest is contraindicated in patients with a history of hypersensitivity to Megestrol Acetate or any component of the formulation.

Warnings and Precautions
Use in Pregnancy
Category D

The use of progestational agents during the first four months of pregnancy is not recommended.

Overdosage
No serious side effects have resulted from studies involving Megestrol Acetate administered in dosages as high as 1600 mg/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.

Precaution
Use with caution in patients with a history of thromboembolic disease.

Drug Interaction
Due to the significant decrease in the exposure of indinavir by Megestrol Acetate, administration of a higher dose of indinavir should be considered when co administering with Megestrol Actate.

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, vomiting, edema and breakthrough uterine bleeding occur in approximately 1% to 2% of patients. Dyspnea, pain, Heart failure, hypertension, hot flushes, sweating, mood changes, cushingoid facies, tumor flare (with or without hypercalcemia), hyperglycemia, alopecia, carpal tunnel syndrome, asthenia, malaise, lethargy, rash, flatulence, diarrhoea and impotence have been reported. Constipation and urinary frequency have been reported in patients who received high doses of Megestrol Acetate in clinical trials.A rarely encountered side effect of prolonged administration of Megestrol Acetate is urticaria, presumably an idiosyncratic reaction to the drug. Mezest is contraindicated as a diagnostic test for pregnancy.

PHARMACEUTICAL INFORMATION
Storage Conditions
Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging
Mezest 40 Tablet: Each commercial box contains 20 tablets in Alu-Alu blister pack
Mezest 160 Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.

Manufactured By
BEACON Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

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