Cleo® 35

Cyproterone acetate and Ethinylestradiol Tablet

Description
Cleo® 35 is a combination of Cyproterone acetate and Ethinylestradiol which is an antiandrogen-estrogen for use in the treatment of androgen-dependent dermatological conditions in females.

Mechanism of action
Cyproterone is a steroid compound with potent antiandrogenic, progestogenic and antigonadotrophic activity. It exerts its antiandrogenic effect by blocking androgen receptors. It also reduces androgen synthesis by a negative feedback effect on the hypothalamo-pituitary-ovarian systems. The estrogen component (Ethinylestradiol) of Cleo® 35 increases levels of sex hormone binding globulin (SHBG) and thus reduces the free circulating plasma levels of androgens. Cyproterone has no tendency to reduce SHBG levels.
If used alone in women, Cyproterone leads to menstrual cycle disturbances which are avoided when combined with Ethinylestradiol. When Cleo® 35 is administered in a cyclic manner, it has the added effect of preventing ovulation and possible conception.
The components of Cleo® 35 are rapidly absorbed after oral administration. Due to the long terminal half-life of Cyproterone, a 4-fold increase in plasma levels occurs after 6 to 12 days of daily dosing. Long-term therapy (36 months) with this product did not have a significant influence on lipid metabolism. A trend to increase plasma cholesterol and triglyceride levels was observed. There was a slight decrease in low density lipoprotein (LDL) with a simultaneous increase in high density lipoprotein (HDL).

Indications
For the treatment of women with severe acne, unresponsive to oral antibiotic and other available treatments, with associated symptoms of androgenization, including seborrhea and mild hirsutism.

Dosage and Administration
Cleo® 35 should not be prescribed solely for its contraceptive properties. If patient compliance is uncertain and contraception is necessary, then a supplementary nonhormonal contraceptive method should be considered.

Cleo® 35 is supplied in blister pack units consisting of 21 tablets; each tablet containing Cyproterone acetate 2 mg and Ethinylestradiol 0.035 mg. Each cycle consists of 21 days on medication and a 7-day interval without medication (3 weeks on, 1 week off).

• First Treatment Course: The patient is instructed to take 1 tablet daily for 21 consecutive days beginning on day 1 of her menstrual cycle. (For the first cycle only the first day of menstrual flow is considered Day 1). The tablets are then discontinued for 7 days (1 week). Withdrawal bleeding should usually occur during the period that the patient is off the tablets. The first cycle will be somewhat shorter than usual, whereas all following cycles will last 4 weeks. The patient should be instructed to take the first tablet from the blister pack out of the section marked with the corresponding day (for example "Mon" for Monday) of the week and swallow it with some liquid. The patient should be instructed to take the tablet at the same time each day.

• Subsequent Courses: The patient begins her next and all subsequent
21-day course of tablets (following the same 21 days on, 7 days off) on the same day of the week that she began her first course. She begins taking her tablets 7 days after discontinuation, regardless of whether or not withdrawal bleeding is still in progress.

Treatment should be continued for several months, since improvement may not be observed for at least 3 months. The need to continue treatment with Cleo™ 35 should be evaluated periodically by the treating physician. Cleo™ 35 should be discontinued 3 to 4 cycles after signs have completely resolved.

Pregnancy should be ruled out before continuing treatment with Cleo® 35 in patients who have missed a menstrual period, if pregnancy is suspected, medication should be discontinued.

Missed dose
If the patient forgets to take a tablet at the usual time, the tablet may be taken within the next 12 hours. If more than 12 hours have elapsed from the time of usual administration, the patient must discard the missed tablet and continue to take the remaining tablets in the pack at the usual time in order to avoid a premature withdrawal bleeding during this cycle. A supplementary nonhormonal method of contraception must be employed until the pack is empty to prevent pregnancy which would necessitate immediate discontinuation of Cleo® 35 treatment.

Side Effects
- Bleeding
- Dizziness
- Depression
- Weight gain
- Headache
- Edema
- Breast pain
- Lactation
- Blood clot
- Gallstones

Contraindications
- Thrombophlebitis, thromboembolic disorders, or a history of these conditions
- Cerebrovascular disorders
- Myocardial infarction or coronary artery diseases
- Active liver disease or hepatic adenomas or carcinomas
- History of cholestatic jaundice
- Known or suspected carcinoma of the breast
- Known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal vaginal bleeding
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields
- When pregnancy is suspected or diagnosed
- Previous or existing liver tumors
- Severe diabetes with vascular changes
- A history of otosclerosis with deterioration during pregnancy.

Warnings
Predisposing Factors for Coronary Artery Diseases: In women with predisposing factors for coronary artery disease (such as cigarette smoking, hypertension; hypercholesterolemia, obesity, diabetes and increasing age), the use of estrogen/progestogen combinations have been reported as an additional risk factor.
After the age of 35 years, estrogen/progestogen combinations should be considered only in exceptional circumstances and when the risk/benefit ratio has been carefully weighed by both the patient and the physician. Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from the use of this class of medication. This risk increases with age and heavy smoking (15 or more cigarettes per day) and is more marked in women over 35 years of age. Women who use such medication should not smoke.
Estrogen/progestogen combinations may cause an increase in plasma lipoproteins and should be administered with caution to women known to have pre-existent hyperlipoproteinemia. Lipid profiles should be determined regularly in these patients.
The combination of obesity, hypertension and diabetes is particularly hazardous to women who are taking this class of medication. To avoid this triad of conditions develop, the patient should be placed on an alternate form of therapy.

Discontinue medication at the earliest manifestation of:

• Thromboembolic and cardiovascular disorders such as: thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis and retinal thrombosis.

The use of estrogen/progestogen-combination products should be avoided in conditions which predispose to venous stasis and to vascular thrombosis, e.g. immobilization after accidents or confinement to bed during long-term illness. Under such conditions other nonhormonal methods of treatment should be considered. For use when surgery is contemplated, see Precautions.

- Visual defects, partial or complete.
- Papilledema, or ophthalmic vascular lesions.
- Severe headache of unknown etiology, or worsening of pre-existing migraine headache.
- Onset of jaundice or hepatitis.
- Itching of the whole body.

Pregnancy: Fetal abnormalities have been reported to occur in the offspring of women who have taken estrogen/progestogen combinations in early pregnancy. Rule out pregnancy as soon as it is suspected.

Lactation: The use of estrogen/progestogen combinations during the period a mother is breast-feeding her infant may not be advisable. The hormonal components are excreted in breast milk and may reduce its quantity and quality. The long-term effects on the developing child are not known.

This drug may cause fluid retention, conditions such as epilepsy.

Precautions
• ***Physical Examination and Follow up:*** Before estrogen/progestogen combinations are used, a thorough history and physical examination should be made including a blood pressure determination. Breasts, liver, extremities, abdomen and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active and a urinalysis should be done.
The first follow up examination should be done 3 months after the initial prescription. Thereafter, examinations should be conducted at regular intervals during long-term treatment and more frequently for those patients at greater risk for adverse effects. At each annual visit examination should include those procedures outlined above that were done at the initial visit.

• ***Hepatic Function:*** Patients who have had jaundice should be given estrogen/progestogen combinations with great care and under close observation.
If there is a clear-cut history of cholestatic jaundice, especially if it occurred during pregnancy, other methods of treatment should be prescribed. The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved. If the jaundice should prove to be cholestatic in type, therapy should not be resumed. In patients taking estrogen/progestogen combinations, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported, Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of estrogen/progestogen combinations. Although these lesions are uncommon, they have caused fatal infra-abdominal hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

• ***Hypertension:*** Patients with essential hypertension whose blood pressure is well controlled may be given the drug but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary.

• ***Migraine and Headache:*** The onset or exacerbation of migraine or the development of headache of a new pattern which is recurrent persistent or severe, requires discontinuation of medication and evaluation of the cause.

• ***Diabetes:*** Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any alterations in carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given estrogen/progestogen combinations under strict medical supervision. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes should be closely observed.

• ***Ocular Disease:*** Progressive astigmatic error possibly leading to keratoconus, has been noted in some myopic women receiving drugs of the estrogen/progestogen class. In women who developed myopia at or near puberty, and in whom myopia stabilized in adult life, estrogen/progestogen combinations after some 6 months of use have increased the refractive error 2 to 3 fold. Women with a family history of myopic astigmatism or keratoconus who are using such therapy may experience rapid advancement of the ocular disorder. Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist and temporary or permanent cessation of wear considered.

• ***Metabolic and Endocrine Diseases:*** In metabolic or endocrine diseases and when metabolism of calcium and phosphorus is abnormal, careful clinical evaluation should precede medication and a regular follow-up is recommended.

• ***Connective Tissue Disease:*** The use of estrogen/progestogen combinations in some women has been associated with positive lupus erythematous cell tests and will clinical lupus erythematosus. In some instances exacerbation of rheumatoid arthritis and synovitis has been observed.

• ***Breasts:*** Although estrogen/progestogen-combination use has not been shown to increase the risk of developing. breast cancer, particular attention should be paid to women who have an immediate family history of this disease and are therefore more prone to its development Careful monitoring is mandatory because, if a breast cancer should develop, estrogen-containing drugs may cause a rapid progression if the malignancy is hormone-dependent. Special judgment should be used is prescribing such medications for women with fibrocystic disease of the breast. Women receiving such medications should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected.

• ***Vaginal Bleeding:*** Persistent irregular vaginal bleeding requires special diagnostic judgment to exclude the possibility of pregnancy or neoplasm.

• ***Fibroids:*** Patients with fibroids (leiomyoma) should be carefully observed. Sudden enlargement, pain or tenderness require discontinuance of medication.

• ***Age:*** In general, women in the later reproductive years gradually assume an increasing risk of circulatory and metabolic complications which becomes more prominent at 35 years of age. In view of this, closer observation, shorter duration of estrogen/progestogen combination use and avoidance of cigarette smoking is advisable. Alternatively, adoption of other means of therapy should be considered for this age group.
Estrogen/progestogen combinations may mask the onset of climacteric.

• ***Emotional Disorders:*** Patients with• a history of emotional disturbances, especially the depressive type, are more prone to have a recurrence of depression while taking estrogen/progestogen combinations. In cases of a serious recurrence, a trial of an alternate method of therapy should be made which may help to clarify the possible relationship.

• ***Laboratory Tests:*** Results of laboratory tests should be interpreted in light of the fact that the patient is taking estrogen/progestogen therapy.

The laboratory tests listed below are modified.

A. Liver function tests: Aspartate serum transaminase (AST): variously reported elevations.
Alkaline phosphatase and gamma glutamine transaminase (GGT): slightly elevated.
B. Coagulation tests: Minimal elevation of test values reported for such parameters as Factors VII, VIII, IX and X.
C. Thyroid function tests: Protein binding of thyroxin is increased as indicated by increased total serum thyroxin concentrations and decreased T3 resin uptake.
D. Lipoproteins: Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions.
E. Gonadotropins: LH and FSH levels are suppressed by the use of estrogen/progestogen therapy. Wait 2 weeks after discontinuing the use of estrogen/progestogen therapy before measurements are made.

• ***Tissue Specimens:*** Pathologists should be advised of estrogen/progestogen therapy when specimens obtained from surgical procedures are submitted for examination.

• ***Return to Fertility:*** After discontinuing therapy, the patient should delay pregnancy until at least 1 normal menstrual cycle has occurred. The patient should be instructed to use a nonhormonal method of contraception during this time period.

• ***Amenorrhea:*** Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following estrogen / progestogen combination therapy. Amenorrhea, especially if associated with breast secretion that continues for 6 months or more after withdrawal warrants a careful assessment of hypothalamic-pituitary function.

• ***Thromboembolic Complications Post-surgery:***
Retrospective studies have reported an increased risk of post-surgery thromboembolic complications in estrogen/progestogen combination users. If feasible, such drugs should be discontinued at least 1 month prior to elective major surgery. Medication should not be resumed until at least 2 weeks after hospital discharge following surgery.

Drug Interactions
Concurrent use of the following drugs may result in reduced efficacy of Cleo® 35 and increased incidence of breakthrough bleeding: Ampicillin, Analgesics, Antihistamines, Antimigraine preparations, Chloramphenicol, Griseofulvin, Isoniazid, Neomycin, Nitrofurantain, Penicillin V, Phenylbutazone, Sulfonamides and Tetracycline.
Concurrent use of anticoagulants with estrogen/progestogen combinations may reduce the anticoagulant effect. Effectiveness of the following drugs may be altered when used concurrently: Antihypertensive, Benzodiazepines (those that undergo oxidative degradation), Beta-adrenergic blockers, Caffeine, Corticosteroids, Hypoglycemic, Phenothiazine, Theophylline, Tricyclic antidepressants and Vitamins.
Concurrent use of the following drugs may reduce the efficacy of Cleo® 35 because of accelerated estrogen metabolism caused by the induction of hepatic enzymes: Carbamazepine, Phenobarbital, Phenytoin, Pyrimidine and Rifampicin.
Diabetics using estrogen/progestogen combinations may require adjustment of their antidiabetic medication.
Concurrent administration of vitamin C (ascorbic acid) with estrogen/ progestogen combinations has been reported to result in a significant rise in plasma Ethinylestradiol levels.
Rule out pregnancy before treatment is begun. Because of the antiandrogenic action of Cleo® 35, feminization of male fetuses has occurred in animal studies and may possibly occur in humans.

Overdose
Symptoms and Treatment: There have been no reports of overdose with Cleo® 35. There are no specific antidotes and treatment should be symptomatic, based on the knowledge of the pharmacological action of the constituents.

Storage condition
Store below 30°C and in dry place. Protect from light. Keep out of the reach of children

Commercial Pack
Cleo® 35 tablet: Each box containing 21 tablets in 1x21's blister strip. Each tablet contains Cyproterone acetate USP 2 mg and Ethinylestradiol USP 0.035 mg.

nuvista
Manufactured by:
Nuvista Pharma Limited
48 Tongi industrial area, Gazipur, Bangladesh
A subsidiary of Beximco Pharmaceuticals Ltd.
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