Divestra®

ڈائی ویسٹرا

(Cyproterone acetate + Ethinyl estradiol)

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains:
Cyproterone acetate (Ph.Eur.)……..2 mg
Ethinyl estradiol (USP)……..0.035 mg

DESCRIPTION
The chemical name of Cyproterone acetate is 17-acetoxy-6-chloro-1α,2α-methylene-4,6-pregnadien-3,20-dione. The molecular formula is $C_{24}H_{29}ClO_4$ and the molecular weight is 416.96.
The chemical name of Ethinyl estradiol is 19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α). The molecular formula is $C_{20}H_{24}O_2$ and the molecular weight is 296.41

SERIOUS WARNINGS AND PRECAUTIONS
Cyproterone acetate+Ethinyl estradiol, as with all Estrogen+Progestogen combinations, is contraindicated in women with thrombophlebitis, thromboembolic disorders, or a history of these conditions. Cyproterone acetate+Ethinyl estradiol users appear to have an elevated risk of venous thromboembolic events compared to users of levonorgestrel-containing combined oral contraceptives. The risk of venous thromboembolic events with Cyproterone acetate+Ethinyl estradiol appears to be similar to desogestrel and drospirenone-containing combined oral contraceptives. During treatment with Cyproterone acetate+Ethinyl estradiol, Estrogen+Progestogen combinations should not be used. Cyproterone acetate+Ethinyl estradiol should not be prescribed for the purpose of contraception alone. Estrogens or progestogens should not be taken during treatment with Cyproterone acetate+Ethinyl estradiol. The need to continue treatment with Cyproterone acetate+Ethinyl estradiol should be evaluated periodically by the treating physician. Cyproterone acetate+Ethinyl estradiol should be discontinued 3 to 4 cycles after signs have completely resolved. Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from the use of Cyproterone acetate+Ethinyl estradiol. 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 this medication should not smoke.

CLINICAL INFORMATION
Indications
Divestra (Cyproterone acetate+Ethinyl estradiol) Tablets are indicated as follows:
• Signs of androgenization, in women such as severe acne (involving inflammation or nodularity or risk of scarring) where prolonged oral antibiotics or local treatment alone has not been successful, or idiopathic hirsutism of mild to moderate degree.
• It will also provide effective oral contraception in this patient group.

If the hirsutism has only recently appeared or has lately intensified to a considerable extent the cause (androgen-producing tumor or an adrenal-enzyme defect) must be clarified by differential diagnosis.

Dosage and Administration
First treatment course
One tablet is to be taken daily for 21 consecutive days beginning on day 1 of the 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).
Subsequent courses
The patient begins her next and all subsequent 21-day course of tablets with (following the same 21 days on, 7 days off) on the same day of the week that the woman began her first course. The course begins with taking tablets for 7 days after discontinuation, regardless of whether or not withdrawal bleeding is still in progress.
Length of Use
Length of use depends on the severity of the symptoms of androgenization and their response to treatment. In general, treatment should be continued for several months, since improvement may not be observed for at least three months. The need to continue treatment with Divestra (Cyproterone acetate+Ethinyl estradiol) should be evaluated periodically by the treating physician. Divestra (Cyproterone acetate+Ethinyl estradiol) should be discontinued 3 to 4 cycles after signs have completely resolved.
Dosage Adjustment
Children and adolescents
Divestra (Cyproterone acetate+Ethinyl estradiol) is only indicated after menarche.
Use in the Elderly
Divestra (Cyproterone acetate+Ethinyl estradiol) is not indicated after menopause.
Patients with hepatic impairment
Divestra (Cyproterone acetate+Ethinyl estradiol) is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal.
Patients with renal impairment
Divestra (Cyproterone acetate+Ethinyl estradiol) has not been evaluated in renally impaired patients.
Administration Requirement
Treatment should be continued for several months. Should there be a recurrence, weeks or months after discontinuation of tablet-taking, treatment with Divestra Tablets may be resumed. In case of a restart of Divestra (Cyproterone acetate+Ethinyl estradiol) Tablets (following a 4-week or greater tablet interval), the increased risk of venous thromboembolism (VTE) should be considered.

Contraindications
• History of or actual thrombophlebitis or thromboembolic disorders
• History of or actual cerebrovascular disorders
• History of or actual myocardial infarction or coronary arterial disease
• Active liver disease
• Previous or existing liver tumors (benign or malignant)
• History of cholestatic jaundice
• Use with the Hepatitis C virus combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir
• 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
• Concomitant use with other Estrogen+Progestogen combinations or estrogens or progestogens alone
• When pregnancy is suspected or diagnosed
• Severe diabetes with vascular changes
• A history of otosclerosis with deterioration during pregnancy
• Hypersensitivity to this drug or to any ingredient in the formulation or component of the container.

Warnings and Precautions
Discontinue Cyproterone acetate+Ethinyl estradiol tablets at the earliest manifestation of the following:
• Thromboembolic and Cardiovascular Disorders such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis.
• Conditions that predispose to Venous Stasis and to Vascular Thrombosis (eg. immobilization after accidents or confinement to bed during long-term illness).
• 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
• Significant Rise in Blood Pressure
• Onset of Severe Depression
• Severe Upper Abdominal Pain or Liver Enlargement
Carcinogenesis and Mutagenesis
Malignancies may be life-threatening or may have a fatal outcome.
Breast Cancer
Increasing age, a strong family history and long-term users are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity, and late age for first full-term pregnancy.
Hepatic Cancer
Recognized 1st line tests for genotoxicity gave negative results, with cyproterone acetate.
Cardiovascular
Predisposing Factors for Coronary Artery Diseases
Cigarette smoking increases the risk of serious cardiovascular side effects and mortality.
Hypertension
Close supervision is required in patients with essential hypertension.
Endocrine and Metabolism
Diabetes
Diabetic patients, or those with a family history of diabetes, should be observed closely.
Lipid Effects
Estrogen+Progestogen combinations may cause an increase in plasma lipoproteins.
Metabolic and Endocrine Diseases
In such disease, careful clinical evaluation and a regular follow-up is recommended.
Genitourinary
Fibroids
Carefully observation is required for enlargement, pain, or tenderness.
Vaginal Bleeding
Persistent irregular vaginal bleeding requires special diagnostic judgement to exclude the possibility of pregnancy or neoplasm.
Hematologic
An increased risk (rare) of arterial and venous thrombotic and thromboembolic diseases.

Interactions
Drugs which may decrease the therapeutic effect of* Cyproterone acetate+*Ethinyl estradiol and increase the incidence of breakthrough bleeding

Class of Compound	Drug	Proposed Mechanism
Antacids		Decreased intestinal absorption of progestogen*.
Antibiotics	Ampicillin, Cotrimoxazole, Penicillin (V)	Enterohepatic circulation disturbance, intestinal hurry.
	Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.
	Chloramphenicol, Metronidazole, Neomycin, Nitrofurantoin, Sulfonamides, Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.
	Troleandomycin	May retard metabolism of Cyproterone acetate+Ethinyl estradiol , increasing the risk of cholestatic jaundice.
Anticonvulsants	Carbamazepine, Ethosuximide, Lamotrigine, Phenobarbital, Phenytoin, Primidone	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestogen and ethinyl estradiol to SHBG.
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of Cyproterone acetate+Ethinyl estradiol may occur.

* Dose two hours apart

Drugs which may decrease the therapeutic effect of Cyproterone acetate+Ethinyl estradiol and increase the incidence of breakthrough bleeding

Class of Compound	Drug	Proposed Mechanism
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces Cyproterone acetate+Ethinyloestradiol efficacy.
HIV Protease Inhibitors	Ritonavir	Induction of hepatic microsomal enzymes.
Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine	Induction of hepatic microsomal enzymes.
Sedatives and Hypnotics	Barbiturates Benzodiazepines Chloral hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.

Modification of Other Drug Action by Estrogen+Progestogen Combinations

Class of Compound	Drug	Modification of Drug Action
Alcohol		Possible increased levels of ethanol or acetaldehyde
Alpha-II adrenoreceptor Agents	Clonidine	Sedation effect increased.
Anticoagulants	All	Increase clotting factors, decrease efficacy. However, Estrogen+Progestogen combinations may potentiate action in some patients.
Anticonvulsants	All	Fluid retention may increase risk of seizures.
Antidiabetic drugs	Oral hypoglycemics and insulin	Combination may impair glucose tolerance and increase blood glucose.
Antihypertensive agents	Guanethidine and methyldopa	Estrogen component causes sodium retention, progestin has no effect.
	Beta blockers	Increased drug effect (decreased metabolism).
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.
	Antipyrine	Impaired metabolism.
	ASA	Effects of ASA may be decreased by the short-term use..
Aminocaproic acid		Theoretically, a hypercoagulable state may occur.
Betamimetic agents	Isoproterenol	Estrogen causes decreased response to these drugs.
Caffeine		The actions of caffeine may be enhanced.
Cholesterol lowering agents	Clofibrate	Their action may be antagonized, may also increase metabolism of clofibrate.
Corticosteroids	Prednisone	Markedly increased serum levels.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.
Direct-acting antiviral (DAA) medicinal products	Ombitasvir, Paritaprevir, Ritonavir, with and without Dasabuvir	Associated with increases in ALT levels 5 to >20 times the upper limit of normal in healthy female subjects and HCV infected women.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.
Phenothiazine tranquilizers	All phenothiazines, reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.
Sedatives and hypnotics	Chlordiazepoxide Diazepam Lorazepam Oxazepam	Increased effect (increased metabolism).
Theophylline	All	Decreased oxidation, leading to possible toxicity.
Tricyclic antidepressants	Clomipramine (possibly others)	Increased side effects: ie. depression
Vitamin B12		Estrogen+Progestogen combinations have been reported to reduce serum levels of Vitamin B12

Substance decreasing the clearance of Cyproterone acetate+Ethinyl estradiol
Strong and moderate CYP3A4 inhibitors such as azole antifungals, verapamil, macrolides, diltiazem and grapefruit juice can increase plasma concenrations of the estrogen or the progestin or both.
Etoricoxib and Vitamin C are known to increase plasma concentrations.

Pregnancy and Breastfeeding
Combination of Cyproterone acetate and Ethinyl estradiol is contraindicated during pregnancy and breastfeeding.
Effects on ability to drive and use machines
Unknown
Adverse Reactions
Common adverse reactions includes headaches, nausea, abdominal pain, weight gain, depressed or altered mood and breast pain or tenderness.
Uncommon adverse reactions include vomiting, diarrhea, fluid retention and migraine.

Overdose
There is no antidote and treatment should be symptomatic.

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Sex hormones and modulators of the genital system, anti-androgens and estrogens. ATC code: G03HB01
Mechanism of action
Cyproterone acetate inhibits the synthesis of androgen by the target cell, as it is a competitive antagonist on the androgen receptor, and it has an anti-gonadotropic effect therefore decreasing androgen blood concentrations. Ethinyl estradiol up-regulates the synthesis of Sex-Hormone-Binding Globulin (SHBG) in plasma which reduces the amount of free, biologically available androgen in the bloodstream, which amplifies the anti-gonadotropic effect of cyproterone acetate.
The contraceptive effect of Cyproterone acetate and Ethinyl estradiol includes the inhibition of ovulation and changes in the cervical secretion. Cyproterone acetate+Ethinyl estradiol is not recommended for contraception alone.
Pharmacokinetic properties
Absorption
Cyproterone acetate
Following oral administration cyproterone acetate is completely absorbed over a wide dose range. Peak serum concentrations of 15 ng/mL are reached at about 1.6 hours after single ingestion. The absolute bioavailability of cyproterone acetate is unknown.
Ethinyl estradiol
Orally administered Ethinyl estradiol is rapidly and almost completely absorbed. Peak serum concentrations of about 71 pg/mL are reached within 1-2 hours. Absolute bioavailability, as a result of presystemic conjugation and first pass metabolism, is approximately 60%.
Distribution
Cyproterone acetate
Cyproterone acetate is almost exclusively bound to serum albumin. Only 3.5 - 4.0 % of the total serum drug concentrations are present as free steroid. The apparent volume of distribution of cyproterone acetate is about 986 ± 437 L.
Ethinyl estradiol
Ethinyl estradiol is highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG. The apparent volume of distribution is approximately 5 L/kg.
Metabolism
Cyproterone acetate
Cyproterone acetate is subject to extensive metabolism. The main metabolite in plasma is known as 15-hydroxy-CPA. The clearance rate from serum is about 3.6 mL/min/kg.
Ethinyl estradiol
Ethinyl estradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinyl estradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The metabolic clearance rate is about 5 mL/min/kg.
Elimination
Cyproterone acetate
Cyproterone acetate serum levels decrease in two phases which are characterised by half-lives of about 0.8 h and about 2.3 to 3.3 days. Cyproterone acetate is partly excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1:2. The half-life of metabolite excretion is about 1.9 days.
Ethinyl estradiol
Ethinyl estradiol serum levels decrease in two phases, the terminal disposition phase is characterised by half-life of approximately 24 hours. Unchanged drug is not excreted, Ethinyl estradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

PHARMACEUTICAL INFORMATION
Shelf life
2 years

Special precautions for storage
- Store below 30^{0}C.
- Protect from light and moisture.
- Keep out of the reach of children.

ہدایات :
۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دوا کو روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

To be sold on the prescription of a registered medical practitioner only.

صرف مستند ڈاکٹر کے لئے پرفروخت کریں۔

Nature and contents of container
Divestra (Cyproterone acetate+Ethinyl estradiol) 2 mg + 0.035 mg tablets are available in a blister pack of 21's (1 x 21's).

MANUFACTURED BY:
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REVISION DATE
February 2020
PIL-DI-0220/1