PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrCYESTRA®-35

cyproterone acetate and ethinyl estradiol tablets
2 mg/0.035 mg

THERAPEUTIC CLASSIFICATION

Acne Therapy

Paladin Labs Inc.
100 Alexis Nihon Blvd, Suite 600
St-Laurent, Quebec
H4M 2P2

Date of Preparation:
January 17, 2019

Version: 6.0

Control # 223341

Table of Contents

^{Pr}CYESTRA$^{®}$-35

cyproterone acetate and ethinyl estradiol tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	2.0 mg cyproterone acetate and 0.035 mg ethinyl estradiol tablets	Lactose For a complete listing see Dosage Forms, Composition and Packaging section.

INDICATION AND CLINICAL USE

CYESTRA-35 (cyproterone acetate and ethinyl estradiol) is indicated for:

- treatment of women with severe acne, with associated symptoms of androgenization, including seborrhea and mild hirsutism.

CYESTRA -35 should be used only when acne is unresponsive to topical therapy and oral antibiotic treatments.

Note: CYESTRA-35 should not be prescribed for the purpose of contraception alone. However, when taken as recommended (see **DOSAGE AND ADMINISTRATION**), CYESTRA-35 will provide reliable contraception in patients treated for the above clinical conditions. If patient compliance is uncertain and contraception is necessary, then a supplementary non-hormonal contraceptive method should be considered.

Geriatrics
CYESTRA-35 is not indicated after menopause.

Pediatrics
CYESTRA-35 is only indicated after menarche.

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 tumours (benign or malignant);

- History of cholestatic jaundice;
- Use with the Hepatitis C virus combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (see **WARNINGS AND PRECAUTIONS**);
- 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. For a complete listing, see the **DOSAGE FORMS, COMPOSITION** and **PACKAGING** section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

CYESTRA-35, as with all estrogen/progestogen combinations, is contraindicated in women with thrombophlebitis, thromboembolic disorders, or a history of these conditions.

CYESTRA-35 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 and ethinyl estradiol appears to be similar to desogestrel- and drospirenone-containing combined oral contraceptives. During treatment with CYESTRA -35, estrogen/progestogen combinations should not be used.

CYESTRA-35 should not be prescribed for the purpose of contraception alone.

Estrogens or progestogens should not be taken during treatment with CYESTRA-35.

The need to continue treatment with CYESTRA -35 should be evaluated periodically by the treating physician. CYESTRA -35 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 CYESTRA -35. 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.

General

Discontinue Medication 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). Non-hormonal treatment for acne should be used until regular activities are resumed. For use of CYESTRA-35 when surgery is contemplated, see **WARNINGS AND 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
- Significant Rise in Blood Pressure
- Onset of Severe Depression
- Severe Upper Abdominal Pain or Liver Enlargement
    - A liver tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement, or signs of intra-abdominal hemorrhage occur in women taking estrogen/progestogen combinations.

Carcinogenesis and Mutagenesis

Malignancies may be life-threatening or may have a fatal outcome.

Breast Cancer

Increasing age and a strong family history 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. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users of estrogen/progestogen combinations (more than eight years) and starters at early age.

Special judgement should be used in 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. A yearly clinical breast examination is also recommended, because, if a breast cancer should develop, drugs that contain estrogen may cause a rapid progression if the malignancy is hormone-dependant.

Hepatic Cancer

Recognized first-line tests of genotoxicity gave negative results when conducted with cyproterone acetate. However, further tests showed that cyproterone acetate was capable of producing adducts with DNA (and an increase in DNA repair activity) in liver cells from rats and monkeys and also in freshly isolated human hepatocytes. The DNA-adduct level in dog liver cells was extremely low. This DNA-adduct formation occurred at systemic exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. One in vivo consequence of cyproterone acetate treatment was the increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats.

The relevance of these findings does not appear to be clinically significant based on the results of a multicentre international liver tumour case control study which demonstrated that there is no evidence of an increased risk of hepatocellular carcinoma associated with contraceptive steroids containing cyproterone acetate, even after long-term use.

Cardiovascular

Predisposing Factors for Coronary Artery Diseases

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. 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.

CYESTRA-35 users are likely to include women with an inherently increased cardiovascular risk such as that associated with polycystic ovary syndrome. Women with androgen-related conditions (eg, severe acne or hirsutism) may also have an inherently increased cardiovascular risk.

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.

Endocrine and Metabolism

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.

Lipid Effects

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.

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.

The combination of obesity, hypertension, and diabetes is particularly hazardous to women who are taking CYESTRA-35. Should this triad of conditions develop, the patient should be placed on an alternate form of therapy for acne.

Genitourinary

Fibroids

Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness requires discontinuation of the use of the medication.

Vaginal Bleeding

Persistent irregular vaginal bleeding requires special diagnostic judgement to exclude the possibility of pregnancy or neoplasm.

Hematologic

Epidemiological studies have suggested an association between the use of estrogen/progestogen combinations and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism, and of cerebrovascular accidents. These events occur rarely.

CYESTRA-35, like all estrogen/progestogen combinations, is associated with an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combination estrogen/progestogen combination or restarts (following a 4-week or greater pill-free interval) the same or a different estrogen/progestogen combination. Data from a large, prospective, 3-armed cohort study suggest

that this increased risk is mainly present during the first 3 months. VTE is life-threatening and is fatal in 1% to 2% of cases.

Based on a review of the published literature, cases of non-fatal VTE ranging in incidence from 1.2 to 9.9 events per 10,000 women-years have been observed in users of CYESTRA-35 (Spitzer 2003).
Since market introduction in 1998 up to 2013, Health Canada has received 95 reports of VTE (deep vein thrombosis, pulmonary embolism, and stroke) equivalent to a reporting rate of 1.07 events per 10,000 women-years. A total of 12 reports of death were identified. It should be noted that reporting rates determined on the basis of spontaneously reported post-marketing adverse events are generally presumed to underestimate the risks associate with drug treatments.

A large, prospective, 3-armed cohort study has shown that the frequency of VTE diagnosis ranges from about 8 to 10 per 10,000 woman-years in users of estrogen/progestogen combinations with low estrogen content (<50 µg ethinyl estradiol). The most recent data suggest that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman-years in nonpregnant, non-estrogen/progestogen combination users and ranges from 20 to 30 per 10,000 pregnant women or postpartum.

Epidemiological studies have suggested that the risk of VTE for cyproterone acetate and ethinyl estradiol appears to be 1.5 to 2 times higher compared to users of levonorgestrel-containing combined oral contraceptives and may be similar to the risk of desogestrel- or drospirenone-containing products.

Overall the risk for VTE in users of estrogen/progestogen combinations with low estrogen content (<50 µg ethinyl estradiol) is two- to three-fold higher than for nonusers of estrogen/progestogen combinations who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

VTE, manifesting as deep venous thrombosis (DVT) and/or pulmonary embolism (PE), may occur during the use of all estrogen/progestogen combinations.

Extremely rarely, thrombosis has been reported to occur in other blood vessels (eg, hepatic, mesenteric, renal, cerebral, or retinal veins and arteries) in estrogen/progestogen combination users. Symptoms of DVT can include: unilateral swelling of the leg or along a vein in the leg; pain or tenderness in the leg, which may be felt only when standing or walking; increased warmth in the affected leg; red or discolored skin on the leg.

Symptoms of PE can include: sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may bring up blood; sharp chest pain which may increase with deep breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. Some of these symptoms (eg, “shortness of breath”, “coughing”) are nonspecific and might be misinterpreted as more common or less severe events (eg, respiratory tract infections).

The risk for arterial thromboembolism (ATE) in users of estrogen/progestogen combinations with low estrogen content (<50 µg ethinyl estradiol) ranges from about 1 to 3 cases per 10,000

woman-years. An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion, or myocardial infarction (MI).

Symptoms of a cerebrovascular accident can include: sudden numbness or weakness of the face, arm, or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include: sudden pain, swelling, and slight blue discoloration of an extremity; acute abdomen.

Symptoms of MI can include: pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; fullness, indigestion or choking feeling; sweating, nausea, vomiting, or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

Arterial thromboembolic events may be life-threatening or may have a fatal outcome.

Other Risk Factors for Venous or Arterial Thromboembolism or of a Cerebrovascular Accident

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low-dose estrogen/progestogen combinations (<0.05 mg ethinyl estradiol).

Hepatic/Biliary/Pancreatic
Hepatic Impairment

CYESTRA-35 is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal. See also section **CONTRAINDICATIONS**.

Hepatic Nodules

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 intra-abdominal hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

Hepatitis C

CYESTRA-35 must be discontinued prior to starting therapy with the Hepatitis C virus (HCV) combination drug regiment ombitasvir, paritaprevir, ritonavir, with or without dasabuvier (see CONRAINDICATIONS and DRUG INTERACTIONS). During clinical trials with ombitasvir, paritaprevir, ritonavir, with and without dasabuvir, ALT elevations 5 to >20 times the upper limit of normal (ULN) were significantly more frequent in healthy female subjects and HCV infected women using ethinyl estradiol-containing medications. CYESTRA-35 can be restarted approximately 2 weeks following completion of treatment with the HCV combination drug regimen.

Jaundice

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 a patient develops jaundice that proves 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.

Immune

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema. Discontinuation of this medication should be considered.

Connective Tissue Disease

The use of estrogen/progestogen combinations in some women has been associated with positive lupus erythematous cell tests and with clinical lupus erythematosus. In some instances exacerbation of rheumatoid arthritis and synovitis have been observed.

Neurologic

Migraine and Headache

The onset or exacerbation of migraine or the development of headache of a new pattern that is recurrent, persistent, or severe, requires discontinuation of medication and evaluation of the cause.

Ophthalmologic

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.

Peri-operative Considerations

Thromboembolic complications - Post-surgery

There is an increased risk of thromboembolic complications in estrogen/progestogen combination users after major surgery. If feasible, such drugs should be discontinued and a non-hormonal method of treatment substituted at least one month prior to major elective surgery.
Such medication should not be resumed until the first menstrual period after hospital discharge following surgery.

Psychiatric

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. Women with premenstrual syndrome (PMS) may have a varied response to estrogen/progestogen combinations, ranging from symptomatic improvement to worsening of the condition.

Renal

Fluid Retention

This drug may cause fluid retention. Conditions such as epilepsy, asthma, and cardiac or renal dysfunction require careful observation.

Renal Impairment

Cyproterone acetate and ethinyl estradiol has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

Sexual Function/Reproduction

Amenorrhea

Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following discontinuation of 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.

Return to Fertility
After discontinuing therapy, the patient should delay pregnancy until at least one normal spontaneous cycle has occurred in order to date the pregnancy. The patient should be instructed to use a non-hormonal method of contraception during this time period.

Special Populations

Pregnant Women

Estrogen/progestogen combinations must not be taken by pregnant women. Rule out pregnancy before treatment is begun. Because of the antiandrogenic action of cyproterone acetate and ethinyl estradiol tablets, feminization of male fetuses has occurred in animal studies and may possibly occur in humans.

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.

Nursing Women

The use of estrogen/progestogen combinations during the period a mother is breastfeeding 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.

Pediatrics

Cyproterone acetate and ethinyl estradiol is only indicated after menarche.

Geriatrics

Cyproterone acetate and ethinyl estradiol is not indicated after menopause. In general, women in the later reproductive years gradually assume an increasing risk of circulatory and metabolic complications which become 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.

Monitoring and Laboratory Tests

Physical Examination and Follow-up

Before estrogen/progestogen combinations are used, a thorough history and physical examination should be performed 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 visit should be done 3 months after the initial prescription. Thereafter, examinations should be performed at regular intervals during treatment and more frequently for those patients at greater risk for adverse effects.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

An increased risk of the following serious adverse reactions has been associated with the use of estrogen/progestogen combinations:

- Arterial and venous thromboembolism
- Cerebral hemorrhage
- Cerebral thrombosis
- Congenital anomalies
- Gallbladder disease
- Hepatic tumours
- Hypertension
- Mesenteric thrombosis
- Myocardial infarction
- Neuro-ocular lesions (eg, retinal thrombosis and optic neuritis)
- Pulmonary embolism
- Thrombophlebitis

The following adverse reactions also have been reported in patients receiving estrogen/progestogen combinations: Nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10 per cent or fewer of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally, as follows:

- Amenorrhea during and after treatment
- Auditory disturbances
- Breakthrough bleeding
- Breast changes (tenderness, enlargement, secretion)
- Cataracts
- Changes in appetite
- Change in cervical erosion and secretion
- Change in corneal curvature (steepening)
- Changes in libido
- Change in menstrual flow

- Change in weight (increase or decrease)
- Chloasma or melasma which may persist
- Cholestatic jaundice
- Chorea
- Cystitis-like syndrome
- Dizziness
- Dysmenorrhea
- Edema
- Endocervical hyperplasias
- Erythema multiforme
- Erythema nodosum
- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Headache
- Hemolytic uremic syndrome
- Hemorrhagic eruption
- Hirsutism
- Impaired renal function
- Increase in size of uterine leiomyomata
- Intolerance to contact lenses
- Loss of scalp hair
- Mental depression
- Migraine
- Nervousness
- Optic neuritis
- Pancreatitis
- Premenstrual-like syndrome
- Porphyria
- Possible diminution in lactation when given immediately postpartum
- Rash (allergic)
- Raynaud's phenomenon
- Reduced tolerance to carbohydrates
- Retinal thrombosis
- Rhinitis
- Spotting
- Temporary infertility after discontinuation of treatment
- Vaginal candidiasis
- Vaginitis

Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular, in women with hereditary angioedema.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Cyproterone acetate and ethinyl Estradiol tablets were generally well tolerated in studies involving 1563 women who were treated for periods of 6 to 36 cycles. The most frequently reported complaint was dysmenorrhea (10.2%) which decreased over time in a manner characteristic of treatment with estrogen/progestogen combinations. Other effects reported were also similar in nature and frequency to those reported with estrogen/progestogen combinations.

ADVERSE EVENTS	NO. OF CYCLES[1]	% FREQUENCY
Dysmenorrhea	23,426	10.2
Breast tension / tenderness	23,814	6.5
Headache	23,810	5.2
Nervousness	23,827	4.4
Chloasma	23,112	4.2
Depressed mood	23,829	3.4
Decreased libido	23,821	3.1
Varicosities	23,829	2.9
Nausea	23,822	1.9
Edema	23,118	1.7
Dizziness	23,340	1.1

[1] Number of cycles evaluated.

Post-market Adverse Drug Reactions

Serious post-marketing adverse reactions reported with cyproterone acetate and ethinyl estradiol tablets include deep venous thrombosis, venous thrombosis with pulmonary embolism, arterial emboli involving the extremities and the spleen, cerebral ischemic vascular accident, cerebral venous thrombosis, sinus thrombosis, retinal vein thrombosis, hypertensive crisis, migraine, pancreatitis, focal nodular hyperplasia of the liver, subcapsular liver hematoma, liver adenoma, hepatocellular carcinoma, primary bile duct carcinoma, hepatitis, liver dystrophy, cholangitis, pseudo- membranous colitis, cholestasis, abdominal pain, epileptic seizures, cerebral tumor symptoms, acute brachiofacial paresis, acute hydrocephalus, manic syndrome, hyperpathia, anaphylactoid reactions, ascites, diabetes mellitus, acute leukemia and breast cancer.

The following non-serious adverse reactions, listed according to body system, have been reported post-marketing:

Cardiovascular system: headaches, migraine, superficial phlebitis, palpitations, flushing.

Gastrointestinal system: focal nodular hyperplasia, liver tumor, hepatitis, jaundice, hepatomegaly without abnormal liver tests, nausea, diarrhea, flatulence, stomatitis, salivary gland swelling.

Genitourinary system: menstrual disorder, ovarian cyst, myoma, cervix dysplasia, vaginitis, urinary tract infection, premature birth, abortion, missed abortion and placenta insufficiency.

Metabolism: abnormal liver enzymes, hyperthyroidism, hyperprolactinemia.
Nervous system: depression, decreased libido, nervousness, insomnia, somnolence, confusion, hypesthesia, paresthesia, seizures (in patients with a history of epilepsy), visual disturbances, symptoms of conjunctival irritation, hearing disorder.

Skin: alopecia, acne, chloasma, exanthema, erythema nodosum, striae, neurodermitis, skin allergy, urticaria, facial edema, pruritis, photosensitivity, pigmentation, dry skin, Herpes zoster, cellulitis, subcutaneous lumps, eczema, livedo, blue spots.

DRUG INTERACTIONS

Overview

The concurrent administration of estrogen/progestogen combinations with other drugs may result in an altered response to either agent. Estrogen/progestogen combinations like cyproterone acetate and ethinyl estradiol may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may either increase (eg, cyclosporine) or decrease (eg, lamotrigine) (see Tables 1 and 2). It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before estrogen/progestogen therapy is prescribed.

No formal drug-drug interaction studies have been conducted with cyproterone acetate and ethinyl estradiol.

Drug-Drug Interactions

In vitro, ethinyestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical studies, administration of hormonal contraceptive containing ethinylestradiol did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g. midazolam) while plasma concentrations of CYP1A2 substrates can increase weakly (e.g. theophylline) or moderately (e.g. melatonin and tizanidine).

Table 1: Drugs Which May Decrease the Therapeutic Effect of Cyproterone acetate and ethinyl estradiol tablet and Increase the Incidence of Breakthrough Bleeding

Class of Compound	Drug	Proposed Mechanism
Antacids		Decreased intestinal absorption of progestogen *.
Antibiotics	Ampicillin	Enterohepatic circulation disturbance, intestinal hurry.

	Cotrimoxazole Penicillin (V)	
	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 and ethinyl estradiol tablets, 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 and ethinyl estradiol tablets may occur.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces cyproterone acetate and ethinyl estradiol tablets efficacy.
HCV Protease Inhibitors	Boceprevir Telaprevir	Remains to be confirmed.
HIV Protease Inhibitors	Ritonavir	Induction of hepatic microsomal enzymes.
Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine	Induction of hepatic microsomal enzymes.
Other Drugs	Analgesics Antihistamines Antimigraine preparations Vitamin E	Reduced efficacy has been reported with estrogen/progestogen combinations. Remains to be confirmed.
Sedatives and Hypnotics	Barbiturates Benzodiazepines Chloral hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.

*Dose two hours apart

Table 2: Modification of Other Drug Action by Estrogen/Progestogen Combinations

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde	Use with caution.
Alpha-II adrenoreceptor Agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	Estrogen/progestogen combinations increase clotting factors, decrease efficacy. However, estrogen/progestogen combinations may	Use another treatment for acne.

		potentiate action in some patients.	
Anticonvulsants	All	Fluid retention may increase risk of seizures.	Use another treatment for acne.
Antidiabetic drugs	Oral hypoglycemics and insulin	Estrogen/progestogen combinations may impair glucose tolerance and increase blood glucose.	Monitor blood glucose. Use another treatment for acne.
Antihypertensive agents	Guanethidine and methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use another treatment for acne.
	Beta blockers	Increased drug effect (decreased metabolism).	Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	
	Antipyrine	Impaired metabolism.	
	ASA	Effects of ASA may be decreased by the short-term use of estrogen/progestogen combinations.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic acid		Theoretically, a hypercoagulable state may occur because estrogen/progestogen combinations augment clotting factors.	Avoid concomitant use.
Betamimetic agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Discontinuing estrogen/ Progestogen combinations can result in excessive drug activity.
Caffeine		The actions of caffeine may be enhanced as estrogen/ progestogen combinations may impair the hepatic metabolism of caffeine.	Use with caution.
Cholesterol lowering agents	Clofibrate	Their action may be antagonized by estrogen/progestogen combinations. Estrogen/ progestogen combinations may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increased serum levels.	Use another treatment for acne.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Direct-acting antiviral (DAA) medicinal products	Ombitasvir, Paritaprevir, Ritonavir, with and without Dasabuvir	Has been shown to be associated with increases in ALT levels 5 to >20 times the upper limit of normal in healthy female subjects and HCV infected women	See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic
Folic acid		Estrogen/progestogen combinations have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine tranquilizers	All phenothiazines, reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose estrogen/ progestogen combinations. If galactorrhea or hyperprolactinemia occurs, use other method.

Sedatives and hypnotics	Chlordiazepoxide Diazepam Lorazepam Oxazepam	Increased effect (increased metabolism).	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic antidepressants	Clomipramine (possibly others)	Increased side effects: ie, depression	Use with caution.
Vitamin B_{12}		Estrogen/progestogen combinations have been reported to reduce serum levels of Vitamin B_{12}	May need to increase dietary intake, or supplement.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Several of the anti-HIV/HCV protease inhibitors (eg, ritonavir, telaprevir, boceprevir) and non-nucleoside reverse transcriptase inhibitors (eg, nevirapine) have been studied with coadministration of estrogen/progestogen combinations; significant changes (increase or decrease) in the mean AUC of the estrogen or progestogen have been noted in some cases. The efficacy and safety of estrogen/progestogen combination products may be affected. Healthcare providers should refer to the label of the individual anti-HIV/HCV protease inhibitor for further drug-drug interaction information.

Substance decreasing the clearance of cyproterone acetate and ethinyl estradiol tablets

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concenrations of the estrogen or the progestin or both.

Entoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4-1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0.035mg ethinylestradiol.

Vitamin C (ascorbic acid) with estrogen/progestogen combinations has been reported to result in a significant rise in plasma ethinyl estradiol levels.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Herbal products containing St. John's wort (Hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Drug-Laboratory Interactions

Results of laboratory tests should be interpreted in light of the fact that the patient is taking estrogen/progestogen therapy. The following laboratory tests could be modified.

Liver Function Tests

Aspartate serum transaminase (AST) - variously reported elevations. Alkaline phosphatase and gamma glutamine transaminase (GGT) - slightly elevated.

Coagulation Tests

Minimal elevation of test values reported for such parameters as prothrombin and Factors VII, VIII, IX and X.

Thyroid Function Tests

Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T3 resin uptake.

Lipoproteins

Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions.

Gonadotropins

LH and FSH levels are suppressed by the use of estrogen/progestogen therapy. Wait two 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 and Papanicolaou smears are submitted for examination.

DOSAGE AND ADMINISTRATION

Dosage Considerations

CYESTRA-35 (cyproterone acetate and ethinyl estradiol) should not be prescribed for the purpose of contraception alone. If patient compliance is uncertain and contraception is necessary, then a supplementary non-hormonal contraceptive method should be considered.

Recommended Dose and Dosage Adjustment

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 four weeks.

The patient should be instructed to take the first tablet from the blister pack out of the section marked with the corresponding day of the week (for example "Mon" for Monday), and swallow it whole 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.

Length of use: The 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 CYESTRA-35 should be evaluated periodically by the treating physician. CYESTRA-35 should be discontinued 3 to 4 cycles after signs have completely resolved.

Should there be a recurrence of symptoms, weeks or months after discontinuation of tablet-taking, treatment with CYESTRA-35 may be resumed. In case of a restart of CYESTRA-35 (following a 4-week or greater tablet-free interval), the increased risk of VTE should be considered (see **WARNINGS AND PRECAUTIONS**).

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

Missed Dose

It is recommended that CYESTRA-35 tablets be taken at the same time each day.

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 non-hormonal method of contraception must be employed until the pack is empty to prevent pregnancy which would necessitate immediate discontinuation of CYESTRA-35 treatment.

Irregular tablet-taking, vomiting or intestinal infections with diarrhea, very rare individual metabolic disturbances or prolonged simultaneous use of certain medical preparations can affect the contraceptive action (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Administration

If spotting or breakthrough bleeding occurs during the 3 weeks in which CYESTRA-35 is being taken, the patient is instructed to continue taking the medication. This type of bleeding usually is transient and without significance. However if the bleeding is persistent or prolonged, the patient is advised to consult her physician.

In exceptional cases, menstruation may fail to occur during the 7-day tablet-free interval. The patient is advised not to resume tablet-taking and to consult her physician.

Although the occurrence of pregnancy is highly unlikely if the tablets are taken according to directions, the possibility of pregnancy should be ruled out before continuing treatment with CYESTRA-35 in patients who have missed a period of withdrawal bleeding. The patient should consult her physician and in the meantime, a supplementary non-hormonal method of contraception should be employed.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Center.

There have been no reports of overdose with cyproterone acetate and ethinyl Estradiol tablets. Symptoms that may occur are nausea, vomiting, and withdrawal bleeding. Withdrawal bleeding may even occur in girls before menarche, if they have accidentally taken the medicinal product. There are no specific antidotes and treatment should be symptomatic, based on the knowledge of the pharmacological action of the constituents.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Cyproterone acetate and ethinyl estradiol tablet is a combination antiandrogen-estrogen for use in the treatment of androgen-dependent dermatological conditions in females.

Cyproterone acetate 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 (ethinyl estradiol) of cyproterone acetate and ethinyl estradiol tablets increases levels of sex hormone binding globulin (SHBG) and thus reduces the free circulating plasma levels of androgens. Cyproterone acetate has no tendency to reduce SHBG levels.

If used alone in women, cyproterone acetate leads to menstrual cycle disturbances which are avoided when combined with ethinyl estradiol. When cyproterone acetate and ethinyl estradiol tablets are administered in a cyclic manner it has the added effect of preventing ovulation and possible conception.

Pharmacodynamics

The components of cyproterone acetate and ethinyl estradiol tablets are rapidly absorbed after oral administration. Due to the long terminal half-life of cyproterone acetate, a 4-fold increase in plasma levels occurs after 6 to 12 days of daily dosing. Long-term therapy (36 months) with cyproterone acetate and ethinyl estradiol tablets did not have a significant influence on lipid metabolism. A trend to increased 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).

Pharmacokinetics

Both constituents of CYESTRA-35 (cyproterone acetate and ethinyl estradiol) are completely absorbed following oral administration of CYESTRA-35. Maximum plasma levels are observed between 30 minutes and 3 hours.

The time course of post-maximum levels is characterized by a biphasic decay of both compounds with plasma elimination half-lives of 2-3 hours and about 2 days for cyproterone acetate;
1-3 hours and about 1 day for ethinyl estradiol. The absolute bioavailability of cyproterone acetate is complete (100%), that of ethinyl estradiol about 40%, due to a considerable first-pass inactivation during the absorption process. The terminal half-life of cyproterone acetate is approximately twice that of other progestogens and results in a stable plasma level of cyproterone acetate upon multiple dosing.

The main metabolite of cyproterone acetate in the plasma was identified as 15β-OH-cyproterone acetate.

30% of cyproterone acetate and its metabolites are excreted via the urine and 70% via the feces with an excretion half-life of about 2 days. The respective values for ethinyl estradiol and its metabolites are 40% (urine) and 60% (feces) with an excretion half-life of 1 day.

Both steroids are excreted into the breast-milk leading to an estimated daily exposure for a breast-fed infant of about 0.2% cyproterone acetate and 0.02% ethinyl estradiol of the mother's dose.

A 21-day pharmacokinetic study of the once-daily administration of cyproterone acetate and ethinyl estradiol tablets (2 mg cyproterone acetate and 0.035 mg ethinyl estradiol) was conducted in smoking and non-smoking women (8 patients/group). Both components were rapidly absorbed from the formulation. Due to the long half-life of cyproterone acetate, the minimum plasma concentration rose approximately 4-fold and reached steady state after 6-12 days of dosing. The area under the curve (0-24h) between the 21st and the 1st day showed a three-fold increase. No differences in ethinyl estradiol plasma levels were noted between day 1 and day 21 of the study. Ethinyl estradiol was able to induce a 2-fold and 4-fold increase of corticosteroid binding globulin (CBG) and sex hormone binding globulin (SHBG) respectively. No differences were noted between smoking and non-smoking women.

STORAGE AND STABILITY

Store at room temperature (15°C - 30°C). Protect from light.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions

DOSAGE FORMS, COMPOSITION AND PACKAGING

CYESTRA-35 is supplied in blister pack units consisting of 21 tablets; each tablet containing 2 mg cyproterone acetate and 0.035 mg ethinyl estradiol.

Composition

Each tablet is composed of cyproterone acetate 2 mg, and ethinyl estradiol 0.035 mg. Non-medicinal ingredients are: corn starch, lactose, magnesium stearate, povidone, and talc.

The coating of the tablet is composed of calcium carbonate, glycerol, iron oxide pigment, polyethylene glycol, povidone, sucrose, talc, titanium dioxide and wax.

Availability of Dosage Forms

CYESTRA-35 tablets are yellow, round, biconvex and sugar-coated. CYESTRA-35 tablets are available in 21-day blister pack units.

PART II: SCIENTIFIC INFORMATION

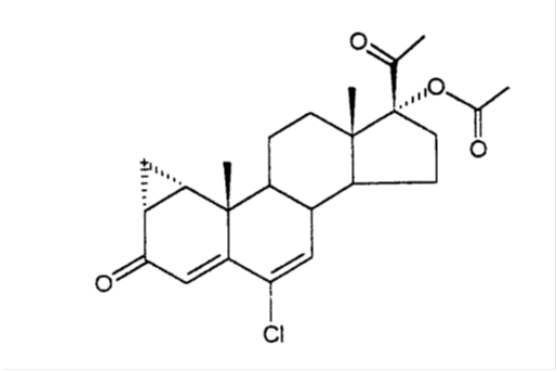
PHARMACEUTICAL INFORMATION

Drug Substance

Cyproterone acetate:

Proper name:	cyproterone acetate (INN)
Chemical name:	6-chloro-1α, 2α -methylene-3, 20-dioxopregna-4,6-dien- 17-yl acetate 6-chloro-3,20-dioxo-1β,2β-dihydro-3`H-cyclopropal[1,2] pregna-1,4,6-trien-17-yl acetate
Molecular formula and molecular mass:	$C_{24}H_{29}ClO_4$ 416.9 g/mol

Structural formula:

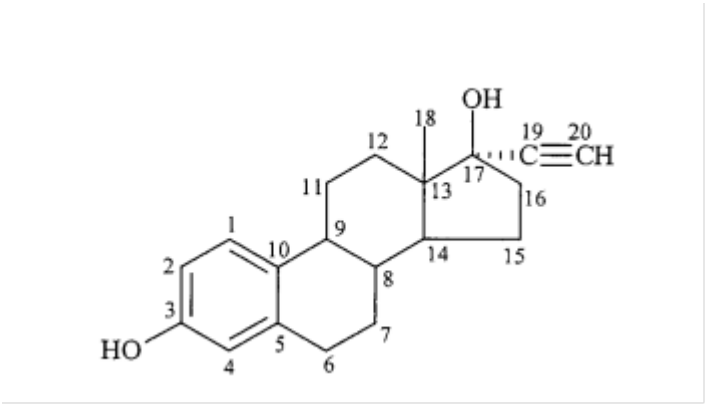


Physiochemical properties:	A white or almost white crystalline powder. Practically insoluble in water, very soluble in methylene chloride, freely soluble in acetone, soluble in methanol, sparingly soluble in ethanol.

Ethinyl Estradiol:

Proper name:	Ethinyl estradiol (USAN)
Chemical name:	19-Nor-17 α-pregna-1,3,5(10)-trien-20-yne-3,17ß-diol 17α-Ethynlestra-1,3,5(10)-triene-3,17ß-diol 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-
Molecular formula and molecular mass:	C20H24O2 296.41 g/mol

Structural formula:



Physiochemical properties:	White to practically white crystals or powder. Insoluble in water, soluble in alcohol, chloroform, ether, and in alkaline solutions. Melting range is 180-186°C.

CLINICAL TRIALS

Comparative Bioavailability Data

A randomized single-dose, two-period, two-treatment crossover comparative bioavailability study of two formulations, Cyproterone/Ethinyl Estradiol 2 mg/0.035 mg Tablets and Diane®-35 2 mg/0.035 mg Tablets (Berlex, Canada), administered as a single 2 x 2 mg/0.035 mg Cyproterone Acetate/ Ethinyl Estradiol dose in 21 healthy adult female subjects under fasting conditions.

Cyproterone (2 x 2 mg/0.035 mg cyproterone acetate/ethinyl estradiol) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_{72} (ng*h/mL)	174.522 174.617 (20)	176.103 177.655 (19)	99.10	94.72 - 103.69
C_{max} (ng/mL)	20.854 21.410 (27)	21.787 22.652 (28)	95.72	83.95 - 109.13
T_{max}§ (h)	2.06 (31)	1.98 (32)		

* Cyproterone/ Ethinyl Estradiol 2 mg/0.035 mg Tablets
† Diane®-35 2 mg/0.035 mg Tablets (Berlex Canada Inc., Canada); purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only
AUC_I and $T_{1/2}$ are not reported as these parameters could not be accurately estimated due to the long half-life of the active ingredient and the design of the study.

Ethinyl estradiol (2 x 2 mg/0.035 mg cyproterone acetate/ethinyl estradiol) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (pg*h/mL)	2104.89 2214.90 (35)	2104.86 2220.32 (36)	100.00	94.42 - 105.91
AUC_I (pg*h/mL)	2238.86 2366.06 (37)	2223.88 2351.35 (37)	100.67	95.04 - 106.64
C_{max} (pg/mL)	157.73 165.32 (30)	163.22 172.44 (30)	96.64	89.70 - 104.11
T_{max}§ (h)	2.26 (34)	2.29 (48)		
$T_{½}$§ (h)	18.04 (21)	17.47 (17)		

*Cyproterone/ Ethinyl Estradiol 2 mg/0.035 mg Tablets

† Diane®-35 2 mg/0.035 mg Tablets (Berlex Canada Inc., Canada); purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only

Efficacy data from three pivotal clinical trials of 2 mg cyproterone acetate and 0.035 mg ethinyl estradiol tablets therapy includes results from 1462 women with symptoms of androgenization (such as acne, seborrhea and hirsutism) over a period of 23, 549 treatment cycles. Cases of facial acne had an improvement/healing rate with cyproterone acetate and ethinyl estradiol tablets of 38% or better after 3 months of treatment. Steady improvement continued throughout the treatment period, resulting in improvement or normalization of most of the patients after 9 cycles. Assessment after 12 cycles of therapy revealed an improvement/healing rate of 91%, with a complete healing rate of 68%. By treatment cycle 36, all cases of facial acne were completely healed.

A similar efficacy profile was observed in cases of acne located on the back and chest area. Again, 35% to 55% of the patients showed improvement or healing of their condition after 3 months of treatment with cyproterone acetate and ethinyl estradiol tablets. Improvement in condition was noted until treatment termination, when 83% to 100% of patients showed improvement/healing after 9 to 12 months of therapy.

Improvement of associated symptoms of androgenization (seborrhea and hirsutism) also showed improvement over the course of the same 3 clinical trials. By cycle 9, improvement of oily skin and hair was noted in 61% to 87% of the women taking cyproterone acetate and ethinyl estradiol tablets. Significant improvement in hirsutism was slower to occur, however a trend towards improvement was observed consistently throughout the treatment period, without showing signs of plateauing. After 36 cycles of cyproterone acetate and ethinyl estradiol tablets therapy, hirsutism on the face, chest and abdomen remitted in 60%, 95% and 82% of the patients, respectively.

DETAILED PHARMACOLOGY

CYESTRA-35 is composed of two active ingredients: cyproterone acetate and ethinyl estradiol. Both are synthetic steroids with structure and function similar to the endogenous sexual hormones progesterone and estradiol respectively.

ANIMAL PHARMACOLOGY

Cyproterone acetate

Cyproterone acetate is a 17-hydroxyprogesterone derivative and displays potent progestogenic, antigonadotrophic and antiandrogenic properties.

Progestogenic and antigonadotrophic effects:

The compound has been shown to be very effective in all classical test systems evaluating progestogenic activities. The threshold doses to induce transformation of the endometrium in the proliferative phase in the rabbit (Clauberg test) are 0.003-0.01 mg after oral application and 0.003 mg after systemic administration. Its efficacy is approximately 100 times higher than the efficacy of progesterone after systemic application and more than 3000 times higher after oral administration. In the test for maintenance of pregnancy, cyproterone acetate is approximately 100 times more potent than progesterone. It is also effective in suppressing permanent estrous experimentally induced with estradiol undecylate in ovariectomized rats and in increasing vaginal sialic acid content in the vagina of ovariectomized mice.

Like all potent progestogens, cyproterone acetate displays antigonadotrophic activities which can be demonstrated by the inhibition of ovulation test and by the testicular inhibition test. The antiovulatory efficacy of cyproterone acetate after oral or subcutaneous application is approximately 3 times higher than that of progesterone and is comparable to that of norethisterone and norethisterone acetate.

Antiandrogenic effects:

In addition to its progestogenic potency, cyproterone acetate shows antiandrogenic activity. It inhibits the effects of endogenously produced or exogenously administered androgens by competitive binding to the androgen receptors of the target organs. In laboratory animals, cyproterone acetate induces a dose-dependant decrease in the weight of the preputial glands and atrophy of the accessory sex glands (prostate, seminal vesicles) and atrophy of the vas deferens and the epididymis. The compound impairs spermatogenesis in a dose-related manner leading to infertility, but atrophy of the Leydig cells is only slight. In male rats, the onset of puberty is delayed or prevented. Treatment of pregnant rats results in disturbance of the testosterone-dependent sexual differentiation of the male fetuses (intrauterine feminization of varying degrees of severity). In male and female rats, skeletal maturation and longitudinal growth are retarded under the influence of cyproterone acetate. These effects are due to the retardation of sex hormone-dependent (androgen and estrogen-dependant) ossification of the epiphyseal cartilage. Antiandrogens primarily inhibit proliferation of peripheral sebaceous gland cells. Treatment of intact male gerbil or castrated androgen-substituted gerbil with cyproterone acetate leads to drastic restriction of sebaceous gland function.

Ethinyl estradiol

Ethinyl estradiol is a potent estrogen with qualities similar to estradiol. In contrast to the latter compound, it is highly effective after oral administration. The relative oral potency of ethinyl estradiol's antigonadotrophic and antifertility effects (eg inhibition of ovulation, inhibition of implantation) is 3-30 times higher than that of orally administered estradiol.

Ethinyl estradiol also exhibits effects on carbohydrate, protein and lipid metabolism similar to those of other estrogens; in rats, hepatic glycogen content and serum triglycerides are significantly increased, whereas serum cholesterol is decreased. In addition, a small but significant increase in the liver weight can be seen. Phospholipids were also raised after treatment for 1 month. The effects on lipid and carbohydrate metabolism may be attributed to an

indirect glucocorticoid activity of estrogens. It is well established that estrogens in the rat cause a stimulation of the adrenals and a depletion of corticoids. The increased glucocorticoid level may be responsible for an induction of gluconeogenesis concomitant with high fasting blood glucose levels.

HUMAN PHARMACOLOGY

The following actions, which are associated with the antiandrogenic effects of cyproterone acetate, have been described in women: inhibition of sebaceous gland activity; suppression of signs of androgenization and other associated symptoms.

Cyproterone acetate is also a potent progestogen and has an antigonadotrophic effect. It intervenes with the hypothalamo-pituitary pathway, causing an inhibition of increased secretion of LH.

TOXICOLOGY

Ethinyl estradiol

See **DETAILED PHARMACOLOGY**

Cyproterone acetate

Acute Toxicity Studies

Acute toxicity of cyproterone acetate plus ethinyl estradiol administered in a 40:1 ratio.

Species	Oral (mg/kg)	Intraperitoneal (mg/kg)	Subcutaneous (mg/kg)
Mouse	>3300	>2500	>2500
Rat	>2600	1400[2]	n/d
Dog	>1000[1]	n/d	n/d

[1] No animals died. One female dog experienced bloody vaginal discharge.
[2] Animals experienced apathy. Autopsy revealed erosion of gastric mucous membrane and suspected liver necrosis.
n/d Not determined.

Repeated Dose Toxicity Studies

Two repeated dose toxicity studies were conducted in groups of rats (10/sex/group) and dogs (3/sex/group) to determine the effects of daily oral (gavage) administration for 12 weeks. The

test doses administered were: 0.0, 0.041, 0.41, or 4.1 mg/kg/day of cyproterone acetate plus ethinyl estradiol in a 40:1 ratio.

Rats

Two female rats died during the first 6 weeks of treatment. Autopsy did not reveal any macroscopic changes that were treatment-related. There was a dose-related reduction in weight gain noted in male rats due to impaired efficiency of food utilization. Alopecia was noted in males due to atrophy and reduced numbers of hair follicles.

In female rats, a dose-related decrease in prothrombin index was seen in treated animals at week 11. A significant decrease in total white cell count associated with reduced lymphocyte count was observed in high dose males but was not dose-related.

Lower absolute and relative prostate and seminal vesicle weights in males and uterine, ovarian and adrenal weights in females were observed. No histopathological changes were noted in these organs. Histopathology noted an increase in fat in periportal hepatocytes and a decrease in centrilobular glycogen in males.

Dogs

- Treatment was generally well tolerated. There was no treatment effect nor any clinical signs. Although within normal limits, there was a treatment-related reduction in serum potassium levels after 8 and 12 weeks of dosing. No deaths were reported. The following changes were considered related to treatment:
- Endometrial hyperplasia at all treatment levels.
- Minimal hornification of the vaginal mucosa at the high dose level (4.1 mg/kg/day).
- Abnormally advanced development of mammary glands at all treatment levels in females and at the mid and high dose level in males.
- Suppression of spermatogenesis at the high dose level.
- Increase in connective tissue elements in the epididymis with atrophy of duct epithelium in high dose males.
- Suppression of prostatic glandular development at the mid- and high-dose levels
- Focal hyperplasia of adrenal zona glomerulosa with associated atrophy of zona fasciculata/reticularis in males and females of the high dose group.

Carcinogenicity

Two carcinogenicity studies were conducted in mice and rats with varying doses of cyproterone acetate (CPA) alone and in combination with ethinyl estradiol (EE2). The animals were divided into 7 groups containing equal numbers of males and females as follows:

Dose (mg/kg/day)	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
CPA	0	0.04	0.4	2.0	0.04	0.4	2.0

EE_2	0	0	0	0	0.001	0.01	0.05

The test substances were administered in the food.

Mice

An investigation into the carcinogenic effect of orally administered cyproterone acetate alone or in combination with ethinyl estradiol (cyproterone acetate + ethinyl estradiol in a ratio of 40:1) in the diet of mice was performed over a period of 105 weeks.

Thinning or loss of hair was observed through much of the study in the high dose groups (groups 4 and 7). Body weight gain was slightly reduced in females of group 4 and in males and females of group 7 in comparison to control values. Food consumption was generally similar among the groups.

The following observations were possibly treatment-related: increased incidence of skin masses or nodules, and alopecia among female mice in groups 5, 6 and 7; pituitary enlargement among male and female mice in group 7; liver masses or nodules plus testicular changes among male mice in group 7.

Histological examination revealed compound-related morphologic alterations of a proliferative nature (liver hyperplastic nodules, hypertrophy and/or hyperplasia of hepatocytes or necrosis among female mice and atrophy of prostate and seminal vesicles among male mice in group 7; lobular hyperplasia of mammary glands among males and female mice in group 7) and/or neoplastic nature (adenomas of pituitary origin among male and female mice in group 7, adenocarcinoma of mammary origin among female mice in group 7).

Rats

Cyproterone acetate alone or in combination with ethinyl estradiol was administered to rats in the diet over a period of 104 weeks. Dose levels were as indicated above.

A thinning and/or loss of hair was noted in male animals of group 4 and in males and females of group 7. Reductions in body weight gain and in mean food consumption were observed among males of groups 4, 6 and 7 and females of groups 6 and 7. Decreased mean hemoglobin and hematocrit values at 18 and 24 months as well as slightly decreased mean total erythrocyte count at 24 months were observed for group 7 males. Mean SGOT, SGPT and alkaline phosphatase levels varied slightly or were moderately elevated in treated animals at 3, 6, 12, 18 and 24 months. Reduced urine volumes were noted among treated animals at 18 and 24 months. At 24 months a higher incidence of cataracts was noted in rats of group 7.

Gross macroscopic lesions that were considered related to drug included: an increased incidence of subcutaneous masses and/or nodules; liver discoloration and nodule formation (groups 6 and 7), atrophy of the testis, seminal vesicles and prostate (groups 4, 5, 6 and 7) and enlargement of the pituitary predominantly among males (groups 5, 6 and 7).

Microscopically, alterations in the liver (hyperplasic nodules, bile duct proliferation, increased pigment in the cytoplasm of sinusoidal lining cells and hypertrophy and/or hyperplasia of hepatocytes) were most prevalent in animals of group 7. Lesions in the male reproductive organs and the kidney were also increased among animals of this group. The incidence of mammary neoplasm (adenomas, adenocarcinoma) was increased among males and females of groups 6 and 7.

Mutagenicity

No mutagenic effect of cyproterone acetate was demonstrated in either in vitro (*Salmonella typhimurium*) or in vivo (micronucleus test in the monkey).

Teratology

Two studies were conducted to determine the embryotoxic and feminizing potential of ethinyl estradiol (EE2) plus cyproterone acetate (CPA) using rats and rabbits. The doses used were as follows:

Group	Total Drug (mg/kg/day)	=	EE2 (mg/kg/day)	+	CPA (mg/kg/day)
1	0		0		0
2	0.041		0.001		0.04
3	0.41		0.01		0.4
4	4.1		0.1		4.0

Rats

A combination of ethinyl estradiol and cyproterone acetate was orally administered by gavage to impregnated dams on days 6-15 post coitus to determine their embryotoxic and feminizing potential. After administration of 0.41 and 4.1 mg/kg/day, a slight to moderate reduction in mean body weight gain was observed. An increased number (29%) of fetuses from high dose dams (4.1 mg/kg/day) had skeletal variations considered related to treatment administration. No indication of a possible feminizing action was observed in any of the test groups.

Rabbits

Ethinyl estradiol plus cyproterone acetate was administered by gavage to pregnant rabbits on days 6-18 post coitus to determine their embryotoxic and feminizing potential. After administration of 0.41 and 4.1 mg/kg/day, a slight to severe reduction in mean body weight gain was observed in the dams. Approximately 85% of implanted embryos in the high dose group (4.1 mg/kg/day) were present as resorptions without fetal remains. Mean body weight of live high dose fetuses was also reduced. No indication of a possible feminizing action was observed in any of the test groups.

Special Studies

Two additional studies were conducted to determine the feminizing potential of a combination of ethinyl estradiol (EE2) and cyproterone acetate (CPA) in the rat and the rabbit.

Rats

Groups of 5 inseminated female rats were given 0.0, 0.041, 4.1 or 41 mg/kg/day of ethinyl estradiol plus cyproterone acetate (1:40) intragastrically as a microcrystalline suspension from the 13th to the 20th day post coitus.

A dose-related feminizing effect was observed after administration of 0.41, 4.1 or 41.0 mg/kg/day. In the high dose group, a significantly increased rate of resorption and marked decrease in body weight gain was noted among dams. 100% feminization of the fetuses of the high dose group was also observed.

In view of the antiandrogenic action of cyproterone acetate and the estrogenic action of ethinyl estradiol, the combination leads to a dose-related feminizing effect on male rat fetuses after 0.41 mg/kg/day. The threshold dose for this effect in the rat was determined to be between 0.041 and 0.41 mg/kg/day.

Rabbits

Groups of 5 inseminated female rabbits were given 0.0, 0.041, 0.41, 1.23, 4.1 or 41.0 mg/kg/day of ethinyl estradiol plus cyproterone acetate (1:40) administered intragastrically as a microcrystalline suspension from the 13th to the 29th day post coitus.

The administration of a dose of 0.041 mg/kg/day produced no signs of embryotoxic action either in the dam or in the fetuses.

The administration of 0.41, 1.23, 4.1 or 41.0 mg/kg/day led to pronounced and dose-related embryotoxic action in the form of an increased number of dead fetuses per litter. After administration of 1.23, 4.1 or 41.0 mg/kg/day the number of resorptions increased markedly with the dose. After administration of 41.0 mg/kg/day only resorptions without fetal remains were found.

Parallel to these findings a dose-related reduction in fetal weight (1.23 and 4.1 mg/kg/day) and a marked reduction in body weight gain among high dose dams was observed.

REFERENCES

1. Aydinlik S, Lachnit-Fixson U, Lehnert J. Estrogen-reduced antiandrogens. Double-blind comparative study of Diane 35 and Diane. Fortschr Med 1986; 104:61-64.

2. Aydinlik S, Kaufmann J, Lachnit-Fixson U, Lehnert J. Long-term therapy of signs of androgenization with a low-dosed antiandrogen-oestrogen combination: Diane-35. Clin Trial J 1990; 27(6):392-402.

3. Barth JH, Cherry CA, Wojnarowska F, Dawber RPR. Cyproterone acetate for severe hirsutism: results of a double-blind dose-ranging study. Clin Endocrinol (Oxf) 1991; 35(1):5-10.

4. Binkley KE, Davis A, 3rd. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. J Allergy Clin Immunol 2000; 106 (3):546- 50.

5. Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. Am J Med 2003; 114 (4):294-8.

6. Carlborg L. Cyproterone acetate versus levonogestrel combined with ethinyl estradiol in the treatment of acne. Acta Obstet Gynecol Scand Suppl 1986; 134:29-32.

7. De Cecco L, Capitanio GL, Bertolini S, Croce S, Centonze A. Clinical and metabolic effects of a new estrogen-antiandrogen low dose combination. In: Schindler AE, ed. Antiandrogen- estrogen therapy for signs of androgenization (New developments in biosciences; 3) Walter de Gruyter, Berlin, New York, 1987; 167-173.

8. Erkkola R, Hirovonen E, Luikku J, Lumme R, Mannikko H, Aydinlik S. Ovulation inhibitors containing cyproterone acetate or desogestrel in the treatment of hyperandrogenic symptoms. Acta Obstet Gynecol Scand 1990; 69:61-5.

9. Ernst E, Schmolzl Ch, Matrai A, Schramm W. Hemorheological effects of oral contraceptives. Contraception 1989; 40(5):571-80.

10. Fugere P, Percival-Smith RKL, Lussier-Cacan S, Davignon J, Farquhar D. Cyproterone acetate/ethinyl estradiol in the treatment of acne. A comparative dose-response study of the estrogen component. Contraception 1990; 40(2):225-34.

11. Lidegaard, O. Absolute and attributable risk of venous thromboembolism in women on combined cyproterone acetate and ethinylestradiol. J Obstet Gynaecol Can 2003; 25(7):575- 577.

12. Lidegaard O, Lokkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009;339:b2890.

13. Mildvan D, Yarrish R, Marshak A, Hutman HW, McDonough M, Lamson M, et al. Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women. J Acquir Immune Defic Syndr 2002; 29 (5):471-7.

14. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Arch Intern Med 2001; 161 (20):2417-29.

15. Seaman, HE, de Vries CS, Farmer RDT. Venous thromboembolism associated with cyproterone acetate in combination with ethinylestradiol (Dianette®): observational studies using the UK General Practice Research Database. Pharmacoepidemiology and Drug Safety. 2004; 13: 427-436.

16. Spitzer, WO. Cyproterone acetate with ethinylestradiol as a risk factor for venous thromboembolism: An epidemiological evaluation. J Obstet Gynaecol Can 2003;25(12):1011-8.

17. Spona J, Huber J, Schmidt JB. Ovulation inhibitory effect of SH B 902 AE (Diane-35) - a new antiandrogen-estrogen combination. In: Schindler AE, ed. Antiandrogen-estrogen therapy for signs of androgenization (New developments in biosciences; 3) Walter de Gruyter, Berlin, New York, 1987; 51-58.

18. Van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009; 339: b2921.

19. Vermeulen A, Rubens R. Effects of cyproterone acetate plus ethinylestradiol low dose on plasma androgens and lipids in mildly hirsute or acneic young women. Contraception 1988; 38(4):419-28.

20. Vexiau P, Vexiau-Robert D, Martineau I, Hardy N, Villette JM, Fier J, Cathelineau G. Metabolic effect at six and twelve months of cyproterone acetate (2 mg) combined with ethinyl estradiol (35 µg) in 31 patients. Horm. Meta. Res 1990; 22:241-245.

21. Product Monograph for ^{Pr}Diane-$^{®}$35 (Bayer Inc., Canada); Control No. 201157. Date of Revision: March 16, 2017.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]CYESTRA-35

Cyproterone acetate and ethinyl estradiol tablets

Read this carefully before you start taking **CYESTRA-35** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CYESTRA-35.**

Serious Warnings and Precautions

- Do not use CYESTRA-35 if you have, or have ever had, a blood clot or redness, pain or swelling in your veins. It could have been in the leg, lung, or other part of your body.
- Women who use CYESTRA-35 appear to have a higher risk of blood clots than women who use levonorgestrel-containing birth control pills. The risk of blood clots with CYESTRA-35 appears to be similar to the risk with birth control pills that contain desogestrel and drospirenone. In rare cases, blood clots can lead to death.
- Do not use other estrogens or progestogens (alone or in combination) when taking CYESTRA-35.
- Do not use CYESTRA-35 for the purpose of birth control alone.
- Your doctor will tell you how long you need to keep taking CYESTRA-35. It should be stopped 3 to 4 months after signs have completely resolved.
- Smoking increases the risk of serious side effects on the heart and blood vessels. This occurs in women who use CYESTRA-35 or estrogen/progestogen combinations. Women who use CYESTRA-35 should not smoke.

Do not use CYESTRA-35 if you are taking ombitasvir, paritaprevir, ritonavir, with or without dasabuvir for the treatment of Hepatitis C. Using these drugs at the same time as CYESTRA -35 has the potential to cause liver problems, such as an increase in the ALT liver enzyme. You can usually start CYESTRA-35 about 2 weeks after finishing treatment with this combination of drugs used for Hepatitis C, but always consult with your doctor or pharmacist.

What is CYESTRA-35 used for?

CYESTRA-35 is used to treat women with severe acne along with seborrhea or mild hirsutism. Mild hirsutism is excess hair on the face, chest, abdomen or legs. Seborrhea is a condition associated with excess oily secretions of the skin. It causes scaly, flaky, itchy, and red skin.

CYESTRA-35 should only be used when acne does not respond to other treatments. These include treatments that are put on the skin and oral antibiotics.

How does CYESTRA-35 work?

CYESTRA-35 reduces the activity of the oil-producing skin glands. They play an important role in the development of acne. Treatment with CYESTRA-35 can lead to the healing or improvement of existing acne. This occurs within 3 to 6 months of starting therapy.

What are the ingredients in CYESTRA-35?

CYESTRA-35 contains a progestogen called cyproterone acetate and an estrogen called ethinyl estradiol.

Non-medicinal ingredients: corn starch, lactose, magnesium stearate, povidone, and talc.
Tablet coating: calcium carbonate, glycerol, iron oxide pigment, polyethylene glycol, povidone, sucrose, talc, titanium dioxide and wax.

CYESTRA-35 comes in the following dosage form:

Tablets: 2 mg cyproterone acetate and 0.035 mg ethinyl estradiol.

Do not use CYESTRA-35 if you have or have had any of the following conditions:

- blood clots in the legs, lungs, eyes or another part of the body, or inflammation of the veins (thrombophlebitis)
- problems with your blood clotting system that increase your risk of developing blood clots or if they have occurred in close relatives
- a stroke, or mini-stroke
- a heart attack, angina, heart or coronary artery disease
- disease of the heart valves with complications
- uncontrolled blood pressure
- severe migraine headaches or a history of them. Symptoms can include speech disability or weakness or numbness in any part of your body
- yellowing of your eyes or skin (jaundice)
- liver disease
- liver tumour
- you are taking ombitasvir, paritaprevir, ritonavir, with or without dasabuvir for the treatment of Hepatitis C

- a known or suspected cancer. It can be of the breast, uterus or ovaries. It can be a cancer that grows in response to estrogen
- a known or suspected hormone-dependent disorder
- severe diabetes associated with problems of the blood vessels
- unusual vaginal bleeding without a known reason
- a loss of vision due to blood vessel disease of the eye
- deafness that got worse during a pregnancy
- you are using an estrogen/progestogen combination, or an estrogen, or a progestogen alone
- are pregnant or think you might be pregnant
- you are breastfeeding. CYESTRA-35 passes into breast milk. It may decrease quality and flow
- allergy to cyproterone acetate, ethinyl estradiol, or to any of the other ingredients in CYESTRA-35

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CYESTRA-35. Talk about any health conditions or problems you may have, including if you:

- smoke
- smoke more than 15 cigarettes a day and are over age 35. Your doctor may decide on a different treatment for you
- are overweight
- have a history of breast disease (eg, breast lumps) or a family history of breast cancer
- have an immediate family member who has ever had a blood clot (in the leg, lung or other parts of the body), a heart attack or a stroke at a young age
- have high blood pressure, or a family history of it
- have high cholesterol or if someone in your immediate family has ever had high blood levels of cholesterol or triglycerides (fatty substances)
- have diabetes, or a family history of it
- suffer from migraines (headaches with symptoms such as disturbed vision or nausea)
- have heart or kidney disease
- have a history of liver disease
- have a history of jaundice (yellowing of the skin or eyes), especially if this happened during pregnancy
- have a history of seizures/epilepsy
- asthma or difficulty breathing
- fluid retention (such as swelling of lower legs)
- have a history of depression (sad mood that won't go away)
- wear contact lenses. If you wear contact lenses and develop visual changes or changes in lens tolerance, you should see an ophthalmologist. Temporary or permanent discontinuation of contact lens use should be considered
- are near-sighted or have astigmatism. Estrogen/progestogen combinations can make these problems worse, especially in women who have a family history of myopia
- have uterine fibroids (non-cancerous growths of the uterus)

- have systemic lupus erythematosus, a disease where the immune system injures the body's own organs and tissues. In some women, the use of estrogen/progestogen combinations may lead to worsening of joint and muscle pain
- have an inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- may be pregnant or are breastfeeding
- have any problems with the valves in your heart and/or have an irregular heart rhythm
- have golden brown pigment patches sometimes called 'pregnancy patches' especially on the face (chloasma). If this is the case, avoid direct exposure to sunlight or ultraviolet light
- have polycystic ovary syndrome (a disorder where many small cysts grow on the ovary and may cause irregular menstrual periods, infertility, acne or excess hair growth. This disorder may increase the risk of blood clots)
- have been told that you have a condition called hereditary angioedema or if you have had episodes of swelling in body parts such as hands, feet, face, or airway passages
- menstrual periods that are light or that occur in an irregular pattern
- have a scheduled lab test or surgery. Consult your doctor about stopping CYESTRA-35. It should be stopped for four weeks before surgery. After surgery, wait until you have a full menstrual period before re-starting CYESTRA-35.

Other warnings you should know about:

You should not take CYESTRA-35 for the purpose of birth control alone. If you take it as directed, it will provide reliable birth control. You should not use other hormonal birth control methods when on CYESTRA -35. If you miss a dose of CYESTRA-35, use a non-hormonal birth control to prevent pregnancy.

Do NOT take CYESTRA-35 if you are obese and have high blood pressure, and diabetes. This combination is particularly hazardous. Your doctor should prescribe a different acne treatment for you.

CYESTRA-35 should only be used in women older than 35 in exceptional cases. You and your doctor must decide that the benefits are greater than the risks. You should know that the risk of serious side effects goes up after age 35. You will need to use CYESTRA -35 for a shorter amount of time. You should be seen regularly by the doctor. In addition, you should not smoke.

Breast Cancer

Cancer of the breast may be life-threatening or may result in death.

- The risk of breast cancer goes up with:
- increasing age
- strong family history of breast cancer (mother or sister)
- obesity
- never having children

- having your first full-term pregnancy at a late age
- use of drugs that contain estrogen/progestogen combinations such as CYESTRA-35 for more than 8 years
- using estrogen/progestogen combination drugs at an early age

The risk of breast tumors gradually goes down after stopping the combined pills.

A yearly breast examination by a healthcare professional is recommended. Talk to your doctor about breast self-examination. Tell your doctor right away if you find a new lump or mass.

Liver Cancer

Cancer of the liver may be life-threatening or may result in death.

Tumors caused by cancer and other reasons can occur. These have led to life-threatening internal bleeding. Contact your doctor immediately if you have severe pain or a lump in your abdomen.

Pregnancy

You should NOT use CYESTRA-35 if you are pregnant or think that you may be pregnant. It will not prevent the pregnancy from continuing. It may interfere with the normal development of your baby. If you become pregnant while taking CYESTRA-35, stop taking it immediately and contact your doctor.

Use after pregnancy, miscarriage or an abortion

Talk to your doctor before using CYESTRA-35 after childbirth, miscarriage, or having an abortion.

Pregnancy after stopping CYESTRA-35

If you wish to become pregnant, talk with your doctor. They may recommend that you stop using CYESTRA-35 and delay pregnancy until you have at least one period (menstrual cycle). Contact your doctor for advice and on methods of birth control that may be used during this time.

Tell all healthcare professionals about all the medicines you take. This includes CYESTRA-35 and any other drugs, vitamins, minerals, natural supplements or alternative medicines.

Certain drugs may interact with CYESTRA-35. They can make it less able to prevent pregnancy. Or, they can cause unexpected vaginal bleeding. Healthcare professionals can tell you if you need to use an additional method of birth control while using another medicine and if so, for how long.

The following may interact with CYESTRA-35:

- drugs used for the treatment of epilepsy (eg, carbamazepine, ethosuximide, lamotrigine, phenobarbital, phenytoin, primidone)
- drugs used for the treatment of tuberculosis (eg, rifampin)
- drugs used for the treatment of HIV infections (eg, nevirapine, ritonavir)
- drugs used for the treatment of Hepatitis C virus infections (eg, boceprevir, telaprevir)
- ombitasvir, paritprevir, ritonavir, with or without dasabuvir (used to treat Hepatitis C)
- antibiotics for bacterial infections such as penicillins, tetracyclines, ampicillin, cotrimoxazole, chloramphenicol, metronidazole, neomycin, nitrofurantoin, sulfonamides, and troleandomycin
- antifungals (for the treatment of fungal infections) (griseofulvin)
- anti-coagulants (blood thinners)
- antihypertensive drugs for high blood pressure (eg, guanethidine, methyldopa, beta blockers)
- antidiabetic drugs and insulin (for diabetes)
- antipyretics (eg, acetaminophen, antipyrine, ASA)
- prednisone
- cholesterol-lowering drugs (eg, clofibrate)
- sedatives and hypnotics (eg, barbituates, benzodiazepines, chloral hydrate, glutethimide, meprobamate)
- drugs used to treat upset stomach or heartburn (antacids) (use 2 hours before or after taking CYESTRA-35)
- drugs used to treat allergy (eg, antihistamines)
- drugs used to treat pain (eg, analgesics)
- drugs used to treat migraine (eg,antimigraine preparations)
- drugs used to treat sad mood (eg, clomipramine)
- drugs used to treat bleeding episodes in some people (eg, aminocaproic acid)
- drugs used to stop preterm labour (eg, beta mimetic agents)
- drugs used to treat schizophrenia (eg, phenothiazine tranquilizers)
- drugs used to treat symptoms of blocked airways (eg, theophylline)
- Vitamin E, Vitamin C, Vitamin B12, folic acid
- the herbal remedy St. John’s wort (primarily used for the treatment of depression)
- alcohol
- caffeine

How to take CYESTRA-35:

Take CYESTRA-35 only on the advice of your doctor. You must take the tablets exactly as prescribed. If not taken appropriately, the contraceptive effect may be decreased and you may become pregnant. Your doctor may tell you to take a non-hormonal method of birth control while taking CYESTRA-35.

Usual dose:

Take one tablet at about the same time every day for 21 days. Swallow it whole with some liquid. Continue until the pack is empty. Do not take any medication for the next 7 days.

You must NOT be off the tablets for more than 7 days in a row.

When to start the first pack of pills:

Begin taking tablets on the first day of your period. Take a tablet marked with that day of the week. For example, if your period starts on a Friday, take a tablet marked ‘Fri’.

Unscheduled period or spotting:

During the month, if an "unscheduled" period occurs during the 3 weeks when you are taking CYESTRA-35 tablets, continue taking the tablets. Slight bleeding will usually stop on its own. If the bleeding is heavy, or similar to menstrual bleeding, talk to your doctor. Many women have spotting or light bleeding, or may feel sick to their stomach during the first three months on CYESTRA-35 therapy. If you feel sick, do not stop taking CYESTRA-35. The problem will usually go away. If it does not go away, check with your doctor or clinic.

When you finish a pack:

During the 7 tablet-free days, you should have your period. You will usually get your period 2-4 days after taking the last tablet.

When to start the second and ongoing pack of pills:

The first tablet in the next pack will always be taken on the same day of the week that you first began taking CYESTRA-35. Take this pill as scheduled regardless of whether your period is in progress.

Missed Period:

If bleeding does not occur during the 7 tablet-free days, do not start a new pack of CYESTRA-35. Contact your doctor to rule out pregnancy. To prevent pregnancy, another non-hormonal birth control method must be used.

Length of Use:

Your doctor will tell you how long to keep taking CYESTRA-35. This depends on how severe your symptoms are and how they respond to treatment. In general, treatment should be stopped 3 to 4 cycles after signs have completely resolved.

Restarting CYESTRA-35:

If symptoms return, weeks or months after you stop taking CYESTRA-35, treatment may be restarted by your doctor. Always follow the advice of your doctor. If it has been more than a 4 weeks without taking a CYESTRA-35 tablet, there is an increased risk for blood clots.

Overdose:

Symptoms of overdose may include nausea, vomiting, or vaginal bleeding. Even girls who have not yet had their first menstrual period but have accidentally taken this medicine may experience such bleeding.

If you think you have taken too much CYESTRA-35, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

What to do if you miss tablets:

If you miss tablets at any time, you could get pregnant. The greatest risks for pregnancy are:

- when you start a pack late, or
- when you miss tablets at the beginning or at the very end of the pack.

If you forget to take your tablet at the usual time, you must take it within the next 12 hours. If more than 12 hours have passed discard the missed tablet. Continue to take the remaining tablets in the pack at the usual time. This will prevent you from getting your period early. To prevent pregnancy, another non- hormonal birth control method must be used during this cycle.

Please note: pregnancy is most likely to occur when you have:

- not taken CYESTRA-35 tablets on a regular basis
- vomiting or intestinal problems with diarrhea
- a very rare problem with your metabolism
- ongoing use of other certain drugs while taking CYESTRA-35

If you vomit or have diarrhea you must continue to take the rest of the tablets. To prevent pregnancy another non-hormonal birth control method must be used. This continues for the rest of the cycle.

What are possible side effects from using CYESTRA-35?

These are not all the possible side effects you may feel when taking CYESTRA-35. If you experience any side effects not listed here, contact your healthcare professional. Please also see the box called “Serious Warnings and Precautions.”

Side effects in women taking CYESTRA-35 or estrogen/progestogen combinations may include:

- nausea and vomiting
- pain during your period
- symptoms similar to those you may have before your period such as mood changes or irritability

- changes in your sex drive
- breast tenderness, changes, enlargement, or discharge
- decrease in milk supply in women who are breastfeeding
- headache, dizziness
- nervousness
- development of golden brown patches on the face (chloasma)
- increase or decrease in weight and appetite
- runny or stuffy nose, or sneezing (rhinitis)
- the cervix is the opening of the womb. It can change with growth of tissue or produce vaginal secretions
- difficulty getting pregnant after stopping treatment

CYESTRA-35 can cause abnormal blood test, Papanicolaou (Pap) smear, breast examination, and urine test results. Your doctor will decide when to perform tests and interpret the results.

Visit your doctor three months or sooner after your first examination. Afterward, visit your doctor at regular intervals.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM			
Symptom/effect	Talk with your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Blood clot in the leg (deep vein thrombosis): leg warmth, swelling or pain especially when standing or walking. You may have red or discoloured skin on your leg			√
Liver Cancer or Tumor: severe abdominal pain, nausea, vomiting or lump in the abdomen		√	
Breast Cancer: breast lumps		√	
Heart Attack: gradual chest pain, tightness pressure or squeezing. Pain in the arm, jaw or back. Trouble breathing, anxiety, and sweating. Rapid or irregular heartbeat. Upset stomach or heartburn, choking feeling, nausea, and vomiting. Dizziness, and weakness			√
High blood pressure: headache, vision disorders, nausea and vomiting			√
Allergic reaction: Itching of the whole body. Or, rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Depression: Sad mood that won't go away. If you			√

have a history of depression, these drugs may make your depression worse			
Blood clot in the lung (pulmonary embolism): sharp chest pain that may increase with deep breathing, coughing up blood, or sudden shortness of breath, or rapid breathing. Anxiety, dizziness, rapid or irregular heartbeat			√
Blood clot in the eye: Sudden partial or complete loss of vision			√
Stroke or blood clot in the brain: Sudden severe headache, vomiting, confusion, loss of balance or coordination, sudden trouble walking, dizziness, fainting with or without seizure, problems with your vision or speech or understanding, weakness or numbness in the face, arm or leg especially on one side of the body.			√
Unexpected, irregular vaginal bleeding, lack of a period or bleeding between periods, especially if you also have secretions from your breast		√	
Edema: Unusual swelling of the arms, hands, legs or feet, face or airway passages		√	
Jaundice or Hepatitis: Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite			√
Other signs of a blood clot can include: sudden pain, swelling, and slight blue discoloration of your hands or feet; sudden, severe pain in your abdomen			√
UNKNOWN			
Severe Headache or Worsening of your Migraine			√
Gallstones: an attack often happens after a fatty meal. It may have intense pain in the upper abdomen, nausea, and vomiting	√		
Abdominal cramps and bloating	√		
Increase in size of uterine leiomyomata (non-cancerous growths in the wall of the uterus): increased abdominal pain and vaginal bleeding	√		
Reduced tolerance to carbohydrates (increased blood sugar levels in diabetics or people who are at risk for diabetes): frequent urination, thirst and hunger	√		
Vaginal yeast infection, Vaginitis (inflammation of the vagina): itching, burning, or discharge from the vagina		√	
Difficulty wearing contact lenses, change in the shape of your cornea, cataracts (cloudy vision)**, optic neuritis** (eye pain or changes in vision)	√		

Chorea: abnormal or uncontrolled movements of the arms or legs		√	
Cystitis-like syndrome (bladder infection): frequent or urgent urination, pain or burning when urinating, foul-smelling urine, cloudy or bloody urine		√	
Hirsutism: excess hair on the face, chest, abdomen or legs	√		
Loss of scalp hair	√		
Erythema multiforme: skin reaction causing a rash or red lumps	√		
Erythema nodosum: skin condition causing reddish, painful lumps, usually on the legs	√		
Hemorrhagic eruption (bleeding under the skin): red or purple spots, or patches	√		
Porphyria (a disease affecting the function of blood): confusion, severe abdominal pain, heart palpitations, trouble breathing, or red/brown urine	√		
Impaired kidney function: mental confusion, fatigue, muscle cramps, increased urination, swelling of the ankles or feet		√	
Raynaud's phenomenon (reduced blood flow): discoloration of your fingers or toes	√		
Auditory disturbances: changes in hearing		√	
Hemolytic uremic syndrome (abnormal breakdown of the blood cells which can clog the kidney): bloody diarrhea or urine, vomiting, abdominal pain, fatigue, confusion, or swelling of the face, hands, or feet		√	
Pancreatitis (inflammation of the pancreas): nausea, vomiting or abdominal pain		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http:// www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
    - Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage

Store at room temperature (15°C - 30°C). Protect from light.

Keep out of reach and sight of children.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines which are no longer required. These measures will help to protect the environment.

If you want more information about CYESTRA-35:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website http://www.paladinlabs.com or by contacting Paladin Labs Inc. at 1-888-867-7426.

This leaflet was prepared by:

Paladin Labs Inc.
100 Alexis Nihon Blvd, Suite 600
St-Laurent, Quebec
H4M 2P2

Date of preparation:
January 17, 2019