

# PRODUCT MONOGRAPH

## PrDIANE<sup>®</sup>-35

cyproterone acetate and ethinyl estradiol tablets

### THERAPEUTIC CLASSIFICATION

Acne Therapy

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#### THERAPEUTIC CLASSIFICATION

Acne Therapy

#### ACTION AND CLINICAL PHARMACOLOGY

DIANE-35 (cyproterone acetate and ethinyl estradiol) 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 DIANE-35 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 DIANE-35 is administered in a cyclic manner it has the added effect of preventing ovulation and possible conception.

The components of DIANE-35 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 DIANE-35 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).

#### INDICATIONS AND CLINICAL USE

**DIANE-35 (cyproterone acetate and ethinyl estradiol) is indicated for the treatment of women with severe acne, unresponsive to oral antibiotic and other available treatments, with associated symptoms of androgenization, including seborrhea and mild hirsutism.**

Note: DIANE-35 should not be prescribed for the purpose of contraception alone. However, when taken as recommended (see **DOSAGE AND ADMINISTRATION**), DIANE-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.

1. DIANE-35, as with all estrogen/progestogen combinations, is contraindicated in women with thrombophlebitis, thromboembolic disorders, or a history of these conditions.
2. DIANE-35 users appear to have an **elevated risk of venous thromboembolic events** compared to users of estrogen/progestogen combinations in some published studies. Estrogen and/or progestogen should not be taken during treatment with DIANE-35.
3. DIANE-35 should **not** be prescribed for the purpose of contraception alone.
4. During treatment with DIANE-35, estrogen/progestogen combinations should not be used.
5. DIANE-35 should be discontinued 3 to 4 cycles after signs have completely resolved.

### CONTRAINDICATIONS

1. History of or actual thrombophlebitis or thromboembolic disorders;
2. History of or actual cerebrovascular disorders;
3. History of or actual myocardial infarction or coronary arterial disease;
4. Active liver disease;
5. Previous or existing liver tumours (benign or malignant);
6. History of cholestatic jaundice;
7. Known or suspected carcinoma of the breast;
8. Known or suspected estrogen-dependent neoplasia;
9. Undiagnosed abnormal vaginal bleeding;
10. Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields;
11. When pregnancy is suspected or diagnosed;
12. Severe diabetes with vascular changes;
13. A history of otosclerosis with deterioration during pregnancy;
14. Known or suspected hypersensitivity to any of the components of Diane-35.

### WARNINGS

#### 1. 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.**

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from the use of DIANE-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.

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.

DIANE-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 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 DIANE-35 (Spitzer 2003).

Since market introduction in 1998 to 2003, Health Canada has received 11 reports of VTE (deep vein thrombosis, pulmonary embolism, and stroke) equivalent to a reporting rate of 0.33 events per 10,000 women-years. One of these cases involved a death. 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.

Overall the risk for venous thromboembolism (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.

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, 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. There is no consensus as to whether the occurrence of these events is associated with the use of estrogen/progestogen combinations.

Symptoms of deep venous thrombosis (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 pulmonary embolism (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 (ATE) 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 fatal.

Women with androgen-related conditions (eg, severe acne or hirsutism) may have an inherently increased cardiovascular risk.

Estrogen/progestogen combinations may cause an increase in plasma lipoproteins and should be administered with caution to women known to have pre-existent hyperlipoproteinemia. Lipid profiles should be determined regularly in these patients.

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

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).

2. **Discontinue Medication at the Earliest Manifestation of the Following:**
  - A. **Thromboembolic and Cardiovascular Disorders** such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis.
  - B. **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 DIANE-35 when surgery is contemplated, see **PRECAUTIONS**.
  - C. **Visual Defects - Partial or Complete**
  - D. **Papilledema, or Ophthalmic Vascular Lesions**
  - E. **Severe Headache of Unknown Etiology, or Worsening of Pre-existing Migraine Headache**
  - F. **Onset of Jaundice or Hepatitis**
  - G. **Itching of the Whole Body**
  - H. **Significant Rise in Blood Pressure**
  - I. **Onset of Severe Depression**
  - J. **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.
3. 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.
4. 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.

5. This drug may cause fluid retention. Conditions such as epilepsy, asthma, and cardiac or renal dysfunction require careful observation.
6. 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.

## PRECAUTIONS

### 1. **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.

### 2. **Hepatic Function**

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. 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.

**Hepatic Impairment**

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

**3. 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.

**4. 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.

**5. 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.

**6. Renal Impairment**

Diane-35 has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

**7. 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.

**8. 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.

**9. Connective Tissue Disease**

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

**10. Breasts**

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.

**11. Vaginal Bleeding**

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

**12. Fibroids**

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

**13. Age**

**Pediatric Use**

Diane-35 is only indicated after menarche.

**Elderly**

Not applicable. Diane-35 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.

**14. 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.

**15. Laboratory Tests**

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.

**A. Liver Function Tests**

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

**B. Coagulation Tests**

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

**C. Thyroid Function Tests**

Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T<sub>3</sub> resin uptake.

**D. Lipoproteins**

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

**E. Gonadotropins**

LH and FSH levels are suppressed by the use of estrogen/progestogen therapy. Wait two weeks after discontinuing the use of estrogen/progestogen therapy before measurements are made.

**16. Tissue Specimens**

Pathologists should be advised of estrogen/progestogen therapy when specimens obtained from surgical procedures and Papanicolaou smears are submitted for examination.

**17. 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.

**18. 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.

**19. 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.

**20. Drug Interactions**

The concurrent administration of estrogen/progestogen combinations with other drugs may result in an altered response to either agent. Estrogen/progestogen combinations like DIANE-35 may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may either increase (eg, cyclosporine) or decrease (eg, lamotrigine) (see [Table 1](#) and [Table 2](#)). It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before estrogen/progestogen therapy is prescribed.

**21. Pregnancy**

Estrogen/progestogen combinations must not be taken by pregnant women. Rule out pregnancy before treatment is begun. Because of the antiandrogenic action of DIANE-35, feminization of male fetuses has occurred in animal studies and may possibly occur in humans.

**22. Immune**

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

**Table 1: Drugs Which May Decrease the Therapeutic Effect of Diane-35 and Increase the Incidence of Breakthrough Bleeding**

Class of Compound	Drug	Proposed Mechanism
Anticonvulsants	Carbamazepine Ethosuximide Phenobarbital Phenytoin Primidone Lamotrigine	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.

**Table 1: Drugs Which May Decrease the Therapeutic Effect of Diane-35 and Increase the Incidence of Breakthrough Bleeding**

Class of Compound	Drug	Proposed Mechanism
Antibiotics	Ampicillin Cotrimoxazole Penicillin (V)	Enterohepatic circulation disturbance, intestinal hurry.
	Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.
	Troleandomycin	May retard metabolism of DIANE-35, increasing the risk of cholestatic jaundice.
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of DIANE-35 may occur.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces DIANE-35 efficacy.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.
Antacids		Decreased intestinal absorption of progestins*.
Other Drugs	Phenylbutazone Antihistamines Analgesics Antimigraine preparations Vitamin E	Reduced efficacy has been reported with estrogen/progestogen combinations. Remains to be confirmed.
HIV Protease Inhibitors	Ritonavir	Induction of hepatic microsomal enzymes.
Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine	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 adrenoceptor Agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	Estrogen/progestogen combinations increase clotting factors, decrease efficacy. However, estrogen/progestogen combinations may potentiate action in some patients.	Use another treatment for acne.
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 methyl dopa	Estrogen component causes sodium retention, progestin has no effect.	Use another treatment for acne.

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

Class of Compound	Drug	Modification of Drug Action	Suggested Management
	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.
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 Lorazepam Oxazepam Diazepam	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 <sub>12</sub>		Estrogen/progestogen combinations have been reported to reduce serum levels of Vitamin B <sub>12</sub>	May need to increase dietary intake, or supplement.

Several of the anti-HIV protease inhibitors (eg, ritonavir) and non-nucleoside reverse transcriptase inhibitors (eg, nevirapine) have been studied with coadministration of estrogen/progestogen combinations; significant changes (increase and decrease) in the mean AUC of the estrogen and progestogen and the potential to affect hepatic metabolism 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 protease inhibitor for further drug-drug interaction information.

No formal drug-drug interaction studies have been conducted with DIANE-35.

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

## **ADVERSE REACTIONS**

### **General**

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

- thrombophlebitis
- arterial thromboembolism
- pulmonary embolism
- mesenteric thrombosis
- neuro-ocular lesions (eg, retinal thrombosis and optic neuritis)
- myocardial infarction
- cerebral thrombosis
- cerebral hemorrhage
- hypertension
- hepatic tumours
- gallbladder disease
- congenital anomalies

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:

- Gastrointestinal symptoms (such as abdominal cramps and bloating),
- Breakthrough bleeding,
- Spotting,
- Change in menstrual flow,
- Dysmenorrhea,
- Amenorrhea during and after treatment,
- Temporary infertility after discontinuation of treatment,
- Edema,
- Chloasma or melasma which may persist,
- Breast changes (tenderness, enlargement, secretion),
- Change in weight (increase or decrease),
- Change in cervical erosion and secretion
- Endocervical hyperplasias,

- Possible diminution in lactation when given immediately postpartum,
- Cholestatic jaundice,
- Migraine,
- Increase in size of uterine leiomyomata,
- Rash (allergic),
- Mental depression,
- Reduced tolerance to carbohydrates,
- Vaginal candidiasis,
- Premenstrual-like syndrome,
- Intolerance to contact lenses,
- Change in corneal curvature (steepening),
- Cataracts,
- Optic neuritis,
- Retinal thrombosis,
- Changes in libido,
- Chorea,
- Changes in appetite,
- Cystitis-like syndrome,
- Rhinitis,
- Headache,
- Nervousness,
- Dizziness,
- Hirsutism,
- Loss of scalp hair,
- Erythema multiforme,
- Erythema nodosum,
- Hemorrhagic eruption,
- Vaginitis,
- Porphyria,
- Impaired renal function,
- Raynaud's phenomenon,
- Auditory disturbances,
- Hemolytic uremic syndrome,
- Pancreatitis.

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

### **Product Specific Adverse Reactions**

DIANE-35 (cyproterone acetate and ethinyl estradiol) was 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 <sup>1</sup>	% 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

<sup>1</sup> Number of cycles evaluated.

Serious post-marketing adverse reactions reported with DIANE-35 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.

## **SYMPTOMS AND TREATMENT OF ACUTE OVERDOSAGE**

For management of suspected drug overdose, contact your regional Poison Control Center.
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There have been no reports of overdose with DIANE-35 (cyproterone acetate and ethinyl estradiol). There are no specific antidotes and treatment should be symptomatic, based on the knowledge of the pharmacological action of the constituents.

## **DOSAGE AND ADMINISTRATION**

DIANE-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.

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

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.

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

Treatment should be continued for several months, since improvement may not be observed with 4 or 5 cycles. DIANE-35 should be discontinued 3 to 4 cycles after signs have completely resolved. Should there be a recurrence, weeks or months after discontinuation of tablet-taking, treatment with DIANE-35 maybe resumed. In case of a restart of DIANE-35 (following a 4-week or greater pill interval), the increased risk of VTE should be considered (see WARNINGS). Pregnancy should be ruled out before continuing treatment with DIANE-35 in patients who have missed a menstrual period. If pregnancy is suspected, medication should be discontinued.

### Special Notes on Administration

It is recommended that DIANE-35 tablets be taken at the same time each day. Irregular tablet-taking, vomiting or intestinal affections with diarrhea, very rare individual metabolic disturbances or prolonged simultaneous use of certain medical preparations can affect the contraceptive action (see Drug Interactions under **PRECAUTIONS**).

If spotting or breakthrough bleeding occurs during the 3 weeks in which DIANE-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 DIANE-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.

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 DIANE-35 treatment.

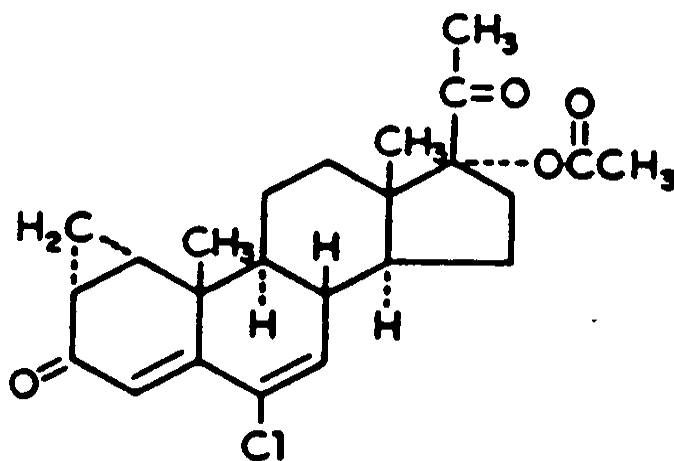
**Use of the blister pack:** The patient should be instructed to take the first tablet from the blister pack out of the section marked with the corresponding day of the week (for example "MO" for Monday), and swallow it whole with some liquid. The patient should be instructed to take the tablet at the same time each day.

**PHARMACEUTICAL INFORMATION**Drug Substance

Trade Name: DIANE-35

Proper Name: Cyproterone acetate (INN)  
Ethinyl estradiol (USP)Cyproterone acetate:Chemical Name: 17-acetoxy-6-chloro-1 $\alpha$ ,2 $\alpha$ -methylene-4,6-pregnadien-3,20-dione

Structural Formula:

Molecular Formula:  $C_{24}H_{29}ClO_4$ 

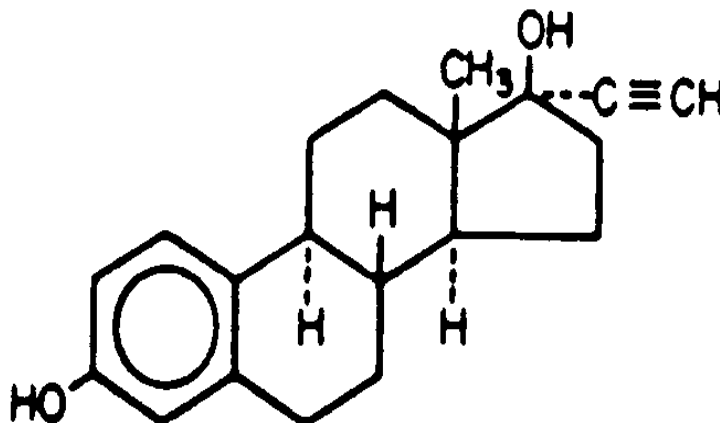
Molecular Weight: 416.95

Description: White to faintly yellow powder. Insoluble in water, freely soluble in chloroform and dioxane. Melting range is 206-213°C.

Ethinyl Estradiol:

Chemical Name: 19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17 $\alpha$ )

Structural Formula:



Molecular Formula:  $C_{20}H_{24}O_2$

Molecular Weight: 296.41

Description: White to slightly yellowish-white crystalline powder. Insoluble in water, soluble in alcohol, chloroform, ether, vegetable oil, and in alkaline solutions. Melting point is 180-186°C.

Composition

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

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

Stability and Storage Conditions

Store at room temperature (15°C - 25°C).

**AVAILABILITY OF DOSAGE FORMS**

DIANE-35 tablets are beige, round, biconvex and sugar-coated.

DIANE-35 tablets are available in 21-day blister pack units.

**INFORMATION FOR THE PATIENT****PATIENT PACKAGE INSERT****DIANE<sup>®</sup>-35****Acne Treatment****Composition**

DIANE-35 is a preparation which contains 2 sex hormones, cyproterone acetate and ethinyl estradiol in a specific ratio. DIANE-35 contains, in each tablet, 2 mg cyproterone acetate and 0.035 mg ethinyl estradiol.

**Warnings**

1. DIANE-35, as with all estrogen/progestogen combinations must not be used in women with thrombophlebitis, thromboembolic disorders (blood clots), or a history of these conditions.
2. DIANE-35 users appear to have an elevated risk of blood clots compared to users of estrogen/progestogen combinations in some published studies.
3. DIANE-35 should not be prescribed for the purpose of birth control alone.
4. Estrogen/progestogen combinations should not be taken during treatment with DIANE-35.
5. DIANE-35 should be discontinued 3 to 4 cycles after signs have completely resolved.
6. You should know that cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from DIANE-35 use. This risk increases with age and heavy smoking (15 or more cigarettes a day) and is more marked in women over 35 years of age. Women who use estrogen/progestogen combinations should not smoke.

**Properties and Indications**

DIANE-35 is a medication for the treatment of women suffering from pronounced forms of acne, accompanied by seborrhea (excess oily secretions of the skin), inflammation or formation of nodes, and mild forms of hirsutism (excess hair on the face, chest, abdomen or legs), and for whom treatment with oral antibiotics or other available treatments has not worked. DIANE-35 is taken in tablet form.

The cyproterone acetate in DIANE-35 reduces the activity of the sebaceous glands which plays an important role in the development of acne. This leads, usually within 3 to 6 months of therapy, to the healing or improvement of existing acne.

You should not take DIANE-35 for the purpose of birth control alone, however, during treatment with DIANE-35, ovulation will not take place if the medication is taken as prescribed (see section "**How to Take DIANE-35**"). Therefore, estrogen/progestogen combinations should not be used during treatment with DIANE-35, but if you are concerned about occasionally missing a dose of DIANE-35, you may wish to use other forms of birth control to avoid becoming pregnant.

This type of medication is not suitable for every woman. In a small number of women, serious side effects may occur. Your doctor can advise you if you have any conditions that would pose a

risk to you. The use of estrogen/progestogen combination tablets should always be supervised by your doctor.

**You should not use Diane-35** if you have or have had any of the following conditions:

- Unusual vaginal bleeding that has not yet been diagnosed.
- Blood clots in the legs, lungs, eyes or elsewhere.
- A stroke, heart attack, or chest pain (angina pectoris).
- Known or suspected cancer of the breast or sex organs.
- Known or suspected hormone-dependent disorders.
- Previous or existing liver tumours.
- Jaundice or liver disease if still present.
- Severe diabetes associated with circulatory problems.
- Disturbances of vision.
- Deterioration of a disorder causing worsening deafness (otosclerosis) during a previous pregnancy.
- An allergic reaction to this medication or to its ingredients (The non-medicinal ingredients in DIANE-35 are calcium carbonate, corn starch, ferric oxide yellow, glycerol, lactose, magnesium stearate, polyethylene glycol, povidone, sucrose, talc, titanium dioxide and wax).
- If you 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.

DIANE-35 should not be taken if you are pregnant, if pregnancy is suspected or if you are breast-feeding.

DIANE-35 should not be taken if you have diabetes and hypertension associated with obesity.

### **When You Are Taking DIANE-35**

If you and your doctor have elected for you to use DIANE-35, you should be aware of the following:

1. Take DIANE-35 only on the advice of your doctor and carefully follow all directions given to you. You must take the tablets exactly as prescribed. If not taken appropriately, the contraceptive effect may be decreased and you may become pregnant.
2. After the age of 35 years, DIANE-35 should be considered only in exceptional circumstances and when the risks and benefits has been carefully weighed by both the patient and the physician.
3. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at regular intervals.
4. **You should be alert for signs of serious adverse effects and call your doctor immediately if they occur:**

- sharp pain in the chest which may increase with deep breathing; coughing blood; sudden shortness of breath or rapid breathing; sense of anxiety; severe light-headedness or dizziness; rapid or irregular heartbeat. These symptoms could indicate a possible blood clot in the lung.
  - pain and/or swelling in the calf 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. These symptoms could indicate a possible blood clot in the leg.
  - crushing chest 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. These symptoms could indicate a possible heart attack.
  - sudden severe or worsening headache or vomiting; sudden trouble walking, dizziness, loss of balance or coordination; loss of consciousness or fainting with or without seizure; sudden confusion, disturbances of vision, speech, or understanding; sudden weakness or numbness of the face, arm, or leg. These symptoms could indicate a possible stroke.
  - sudden pain, swelling, and slight blue discoloration of an extremity; acute abdomen; sudden partial or complete loss of vision. This symptom could indicate a blood clot in the eye.
  - severe pain or lump in the abdomen. These symptoms could indicate a possible tumour of the liver.
  - severe depression
  - yellowing of the skin (jaundice)
  - itching of the whole body
  - rise in blood pressure
  - unusual swelling of the extremities (hands and feet), face, or airway passages
  - breast lumps. **Ask your doctor for advice and instruction on regular self-examination of your breasts.**
5. DIANE-35 should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing and may interfere with the normal development of the baby.
  6. If you wish to become pregnant, your doctor may recommend that you discontinue the use of DIANE-35 and delay pregnancy until at least one spontaneous menstrual cycle has occurred. Contact your doctor for advice on this and for recommendations on appropriate methods of birth control that may be used during this time.
  7. Consult your doctor before resuming the use of estrogen/progestogen combinations after childbirth, miscarriage, or therapeutic abortion. Hormones in estrogen/progestogen combinations are known to appear in the milk and may decrease its flow.
  8. If for any reason you should require **major** elective surgery, the surgeon should be informed that you are using an estrogen/progestogen so that you can be correctly advised

about discontinuing its use one month before surgery and switching to an alternative treatment.

9. **If you see a different doctor, inform him or her that you are taking estrogen/progestogen combination tablets.** Tell the doctor that your estrogen/progestogen combination tablets are DIANE-35.
10. **Inform your doctor if you are taking or if you start to take other medications.** This applies to both prescription and non-prescription drugs, including natural health products. These medications may change the effectiveness and/or cycle control of your estrogen/progestogen combination tablets. **You may need to use a back-up (barrier) method of birth control.**
11. If you have asthma, epilepsy, cardiac or renal disease or fluid retention (such as swelling of lower legs) or any other chronic condition you will require careful observation and should see your doctor frequently.
12. If you wear contact lenses and develop visual changes or changes in lens tolerance you should be assessed by an ophthalmologist and temporary or permanent cessation of wear should be considered.
13. DIANE-35 may interfere with laboratory tests. Should you require such tests, please inform your doctor that you are taking DIANE-35.

Side effects other than those listed here may also occur. Talk to your doctor about any side effect that seems unusual or that is especially bothersome.

### **How to Take DIANE-35**

1. If instructed to do so by your doctor, a non-hormonal method of birth control should be employed while taking DIANE-35.
2. For your first pack of DIANE-35, begin taking tablets on the first day of menstrual bleeding.
3. Take one tablet daily for 21 days; no medication is taken for the next seven days.
4. When receiving any medical treatment, be sure to tell your doctor that you are using DIANE-35.
5. When you have taken all 21 tablets in this pack, wait 7 days and then start a new pack of DIANE-35. During the 7 days that you are not taking any tablets, you should have your period, usually 2-4 days after you have taken your last tablet.
6. The first tablet in every subsequent pack will always be taken on the same day of the week that you first began taking DIANE-35 tablets regardless of whether your bleeding has already ceased (which it usually has) or is still continuing.

**Please note:** Irregular tablet-taking, vomiting or intestinal affections with diarrhea, some very rare individual metabolic disturbances or prolonged simultaneous use of certain medical preparations can affect the efficacy of DIANE-35.

### **Missed Tablets, Vomiting or Diarrhea**

If you forget to take your tablet at the usual time, you must take it within the next 12 hours at the latest. If more than 12 hours have passed from the time that you normally take your tablet, you must discard the missed tablet and continue to take the remaining tablets in the pack at the usual time to prevent premature bleeding.

Also in case of vomiting or diarrhea you must continue to take the remaining tablets. However, a supplementary non-hormonal method of birth control must be used for the remainder of the cycle of use to prevent pregnancy.

### **Overdose**

There have been no reports of serious effects from overdose. Symptoms of overdose may include nausea, vomiting, or vaginal bleeding. In case of drug overdose, contact a health care practitioner, hospital emergency department, or regional Poison Control Center immediately, even if there are no symptoms.

### **Missed Period**

If bleeding fails to occur during the 7 days that you are not taking any tablets, do not start a new pack and contact your doctor to rule out pregnancy.

### **Unscheduled Period**

If an "unscheduled" period occurs during the 3 weeks in which DIANE-35 tablets are being taken, continue taking the tablets. Slight bleeding will usually stop spontaneously. However, if the bleeding is heavy, similar to menstrual bleeding, you should consult your doctor.

7. **Many women have spotting or light bleeding, or may feel sick to their stomach during the first three months on estrogen/progestogen combination therapy.** If you do feel sick, do not stop taking DIANE-35. The problem will usually go away. If it does not go away, check with your doctor or clinic.
8. **If you miss tablets at any time, you could get pregnant.**

With DIANE-35, you are on tablets for 21 days and off tablets for seven days. You must not be off the tablets for more than seven days in a row.

## **PHARMACOLOGY**

DIANE-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 antiovaratory 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.

### **Pharmacokinetics**

Both constituents of DIANE-35 (cyproterone acetate and ethinyl estradiol) are completely absorbed following oral administration of DIANE-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 15 $\beta$ -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 DIANE-35 (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.

### **Clinical Studies**

Efficacy data from three pivotal clinical trials of DIANE-35 (2 mg cyproterone acetate and 0.035 mg ethinyl estradiol) 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 DIANE-35 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 DIANE-35. 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 DIANE-35. 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 DIANE-35 therapy, hirsutism on the face, chest and abdomen remitted in 60%, 95% and 82% of the patients, respectively.

## **TOXICOLOGY**

### **Ethinyl estradiol**

See **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 <sup>2</sup>	n/d
Dog	>1000 <sup>1</sup>	n/d	n/d

<sup>1</sup> No animals died. One female dog experienced bloody vaginal discharge.

<sup>2</sup> 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 (EE<sub>2</sub>). 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 <sub>2</sub>	0	0	0	0	0.001	0.01	0.5

The test substances were administered in the food.

### Mice

An investigation into the carcinogenic effect of orally administered cyproterone acetate or (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 (hyperplastic 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 (EE<sub>2</sub>) plus cyproterone acetate (CPA) using rats and rabbits. The doses used were as follows:

Group	Total Drug (mg/kg/day)	=	EE <sub>2</sub> (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 (EE<sub>2</sub>) 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.

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