

PRODUCT INFORMATION

DIANE®-35 ED

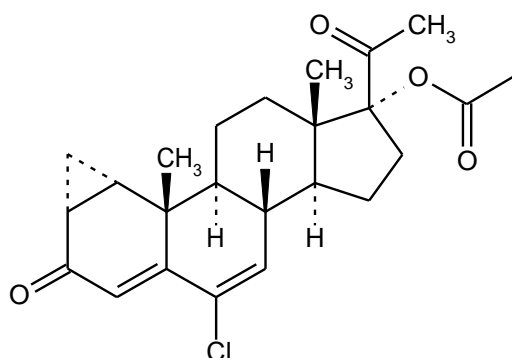
NAME OF THE MEDICINE

DIANE-35 ED is a progestogen-oestrogen combination for the treatment of signs of androgenisation in the woman. At the same time, it is a reliable contraceptive for women who suffer primarily from these signs or in whom acne and similar conditions occur or deteriorate under the use of other ovulation inhibitors.

DIANE-35 ED contains the synthetic progestogen, cyproterone acetate and the synthetic oestrogen, ethinyloestradiol.

Cyproterone acetate:

The chemical name for cyproterone acetate is 6-chloro-17 α hydroxy-1 α ,2 α -methylene-pregna-4,6-diene-3,20-dione acetate and has the following chemical structure:



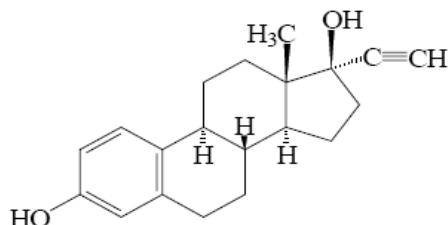
Molecular Formula: C₂₄H₂₉ClO₄

Molecular Mass: 416.96

CAS No: 427-51-0

Ethinyloestradiol:

The chemical name for ethinyloestradiol is 19-nor-17 α -pregna-1,3,5,(10)-triene-20-yne-3,17 β -diol and has the following chemical structure:



Chemical Formula: C₂₀H₂₄O₂

Molecular mass: 296.41

CAS No: 57-63-6

DESCRIPTION

Cyproterone acetate is a white to pale yellow crystalline powder. M.P. 206 - 213°C.

Cyproterone acetate is very soluble in chloroform and dioxane, freely soluble in acetone and benzene, soluble in ethanol, methanol and ethyl acetate, sparingly soluble in solvent hexane and almost insoluble in water.

Ethinylestradiol is a white to slightly yellowish-white, crystalline powder. M.P. 181 - 185°C.

Ethinylestradiol is practically insoluble in water, freely soluble in ethanol (96%) and ether, sparingly soluble in chloroform. It dissolves in dilute alkaline solutions.

Each beige active tablet contains cyproterone acetate 2 mg and ethinylestradiol 35 µg. As well as the active ingredients, DIANE-35 ED tablets also contain the following excipients: lactose, maize starch, povidone, magnesium stearate, sucrose, macrogol 6000, calcium carbonate, purified talc, glycerol, titanium dioxide, iron oxide yellow, glycol montanate, purified water.

Each white placebo tablet contains: lactose, maize starch, povidone, magnesium stearate, sucrose, macrogol 6000, calcium carbonate, purified talc, glycol montanate.

PHARMACOLOGY

Pharmacodynamic Properties

The substance cyproterone acetate contained in DIANE-35 ED blocks the effect of endogenously produced and exogenously administered androgens at the target organs by means of competitive inhibition. This results in a gradual regression of signs of androgenisation, irrespective of whether increased androgen values or increased peripheral sensitivity, are the cause of the disorder. The decrease in androgen concentration at the target organs has an additional therapeutic effect.

While DIANE-35 ED is being taken, the increased sebaceous gland function, which plays an important role in the development of acne and seborrhea, is reduced. This leads - usually after 3 to 4 months of therapy - to the healing of existing acne efflorescences. The excessive greasiness of the hair and skin generally disappears earlier. The loss of hair which frequently accompanies seborrhea likewise diminishes. Treatment with DIANE-35 ED is indicated in women of child-bearing age who exhibit mild forms of hirsutism, and in particular in slightly increased facial hair; results do not, however, become apparent until after several months of use.

Apart from the described antiandrogen effect, cyproterone acetate has also a pronounced progestational action. The combination of ethinylestradiol and cyproterone acetate prevents a possible pregnancy by the inhibition of ovulation, the inspissation of cervical mucus so as to constitute a barrier to sperm, and the rendering of the endometrium unreceptive to implantation.

As well as protection against pregnancy, combined oral contraceptives (COCs) have several positive properties which, next to the negative properties (see PRECAUTIONS, ADVERSE EFFECTS), can be useful in deciding on the method of birth control. For the majority of users, the cycle is more regular, the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. In addition, with the higher-dosed COCs (> 35 µg ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy, endometrial and ovarian cancer. These additional benefits have only been established in case control and cohort studies. Results from randomised controlled trials are not available.

Pharmacokinetics

- **Cyproterone acetate**

Absorption

Following oral administration cyproterone acetate (CPA) is completely absorbed over a wide dose range. Peak serum concentrations of 15 ng/mL are reached at about 1.6 hours after single ingestion. The absolute bioavailability of cyproterone acetate is unknown. Relative bioavailability was calculated, in a study of eight young women, from a dose-corrected comparison of area under the curves (AUC) of serum levels after 100 mg oral and 300 mg intramuscular depot administration and was found to be $80 \pm 30\%$ when averaged over all volunteers (range 23% - 119%).

Distribution

Cyproterone acetate is almost exclusively bound to serum albumin. Only 3.5 - 4.0 % of the total serum drug concentrations are present as free steroid. The ethinyloestradiol-induced increase in sex hormone binding globulin (SHBG) does not influence the serum protein binding of cyproterone acetate. The apparent volume of distribution of cyproterone acetate is about 986 ± 437 L.

Metabolism

Cyproterone acetate is subject to extensive metabolism. The main metabolite in plasma was identified as 15-hydroxy-CPA which is formed possibly via the cytochrome P450 enzyme CYP3A4. The clearance rate from serum is about 3.6 mL/min/kg.

Elimination

Cyproterone acetate serum levels decrease in two phases which are characterised by half-lives of about 0.8 h and about 2.3 to 3.3 days. Cyproterone acetate is partly excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1:2. The half-life of metabolite excretion is about 1.9 days.

Steady-state conditions

Cyproterone acetate pharmacokinetics are not influenced by SHBG levels. Following daily ingestion drug serum levels increase about 2.5-fold reaching steady-state conditions during the second half of a treatment cycle.

- **Ethinylestradiol**

Absorption

Orally administered ethinylestradiol is rapidly and almost completely absorbed. Peak serum concentrations of about 71 pg/mL are reached within 1-2 hours. Absolute bioavailability, as a result of presystemic conjugation and first pass metabolism, is approximately 60%.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of approximately 5 L/kg was determined.

Metabolism

Ethinylloestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylloestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The metabolic clearance rate is about 5 mL/min/kg.

Elimination

Ethinylloestradiol serum levels decrease in two phases, the terminal disposition phase is characterised by half-life of approximately 24 hours. Unchanged drug is not excreted, ethinylloestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state condition

Steady state conditions are reached during the second half of a treatment cycle when serum drug levels are higher by 60% as compared to single dose.

INDICATIONS

DIANE 35 ED is indicated for:

- The treatment of signs of androgenisation in women, such as severe acne (involving inflammation or nodularity or risk of scarring) where prolonged oral antibiotics or local treatment alone has not been successful, or idiopathic hirsutism of mild to moderate degree.
- DIANE-35 ED will also provide effective oral contraception in this patient group. It should not be used in combination with other hormonal contraceptives (see CONTRAINDICATIONS).

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

CONTRAINDICATIONS

Preparations containing oestrogen/progestogen combinations should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during their use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE) (see PRECAUTIONS)
 - Current VTE (on anticoagulants) or history of deep venous thrombosis [DVT] or pulmonary embolism [PE]
 - Known hereditary or acquired predisposition for VTE, such as APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
 - Major surgery with prolonged immobilisation
 - A high risk of VTE due to the presence of multiple risk factors
- Presence or risk of arterial thromboembolism (ATE) (see PRECAUTIONS)
 - Current ATE or history of ATE (e.g. myocardial infarction [MI] or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA])
 - Known hereditary or acquired predisposition for ATE, such as hyperhomocysteinaemia and antiphospholipid-antibodies (e.g. anticardiolipin-antibodies and lupus anticoagulant)
 - History of migraine with focal neurological symptoms
 - A high risk of ATE due to multiple risk factors or to the presence of one serious risk factor such as:
 - diabetes mellitus with vascular symptoms
 - severe hypertension
 - severe dyslipoproteinaemia

- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Use of direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir or dasabuvir and combinations of these (see INTERACTIONS WITH OTHER MEDICINES)
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Concomitant use with another hormonal contraceptive
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Lactation
- Hypersensitivity to any of the ingredients in DIANE-35 ED

DIANE-35 ED is not for use in men.

DIANE-35 ED is composed of the progestogen cyproterone acetate and the oestrogen ethinyloestradiol and is administered for 21 days of a monthly cycle. It has a similar composition to that of a COC. The clinical and epidemiological experience with oestrogen/progestogen combinations like DIANE-35 ED is predominantly based on COCs. Therefore, the following warnings related to the use of COCs apply also for DIANE-35 ED.

PRECAUTIONS

If any of the conditions/risk factors mentioned below are present, the benefits of DIANE-35 ED should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start taking it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide whether DIANE-35 ED should be discontinued.

Circulatory Disorders

Epidemiological studies have suggested an association between the use of COCs containing ethinyloestradiol and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as MI, stroke, DVT and PE. These events occur rarely in average-risk women.

Risk of venous thromboembolism (VTE)

The use of any combined hormonal contraceptive (CHC) increases the risk of VTE compared with no use. The woman should be advised that her VTE risk is highest in the first ever year of use and that there is some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.

Data from a large, prospective 3-armed cohort study (EURAS¹ and LASS²) suggest that this increased risk is mainly present during the first 3 months.

A large, prospective 3-arm cohort study has shown that the incidence rate of VTE ranged from 8 to 10 per 10,000 woman years (WY) in low oestrogen dose (< 50 µg ethinyloestradiol) COC users. The most recent data suggest that the incidence rate of VTE is approximately 4.4 per 10,000 woman years in non-pregnant non-COC users, and ranged from 20 to 30 per 10,000 WY in pregnancy or the post-partum period.

Overall the risk of VTE in users of low oestrogen dose (< 50 µg ethinyloestradiol) COCs are two to threefold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

Epidemiological studies have shown that the incidence of VTE is 1.5 to 2 times higher in users of DIANE-35 than in users of levonorgestrel-containing COCs.

The user group of DIANE-35 is likely to include patients that may have an inherently increased cardiovascular risk such as that associated with polycystic ovarian syndrome.

An additional increase in VTE risk for CHCs containing ≥ 50 µg ethinyloestradiol cannot be excluded.

The increased risk of VTE during the postpartum period must be considered. See DOSAGE AND ADMINISTRATION, Use in Pregnancy and Use in Lactation.

VTE may be life-threatening or may have a fatal outcome (in 1-2% of the cases).

Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see list below).

DIANE-35 is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

When considering risk/benefit, the doctor should take into account that the adequate treatment of a condition may reduce the associated risk of thrombosis.

Risk factors for VTE

- Obesity (body mass index over 30 kg/m²). Risk increases substantially as BMI rises
- Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma
- Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors
- Positive family history (VTE ever in a sibling or parent especially at a relatively early age e.g. before 50)
- Biochemical factors that may be indicative of hereditary or acquired predisposition for VTE include Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency
- Other medical conditions associated with VTE include:
 - Cancer
 - Systemic lupus erythematosus
 - Haemolytic uraemic syndrome
 - Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)
 - Sickle cell disease
- Increasing age, particularly above 35 years
- Smoking

In women at risk of prolonged immobilisation (including major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma), it is advisable to discontinue use of DIANE-35 (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if DIANE-35 ED has not been discontinued in advance.

If a hereditary predisposition to VTE is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in VTE.

Symptoms of VTE (DVT and PE)

Women should be informed of the symptoms of VTE and be advised to seek urgent medical attention if VTE symptoms develop and to inform the healthcare professional that she is taking a CHC.

Symptoms of DVT can include:

- unilateral swelling of the leg and/or foot 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 discoloured skin on the leg

Symptoms of PE can include:

- sudden onset of unexplained shortness of breath or rapid breathing
- sudden coughing which may be associated with haemoptysis
- sharp chest pain or sudden severe pain in the chest which may increase with deep breathing
- severe light headedness or dizziness
- rapid or irregular heartbeat

Some of these symptoms (e.g. “shortness of breath”, “coughing”) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of CHCs with an increased risk for ATE (e.g. MI, angina pectoris, stroke or TIA). Arterial thromboembolic events may be fatal.

The risk of arterial thromboembolic complications in CHC users increases in women with risk factors. DIANE-35 is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

Risk factors for ATE

- Increasing age, particularly above 35 years
- Smoking
- Hypertension
- Obesity
- Positive family history (ATE ever in a sibling or parent especially at relatively early age e.g. below 50)
- Biochemical factors that may be indicative of hereditary or acquired predisposition for ATE include: hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies, and lupus anticoagulant)
- Migraine
- Other medical conditions associated with adverse vascular events:
 - Diabetes mellitus
 - Polycystic ovary syndrome
 - Hyperhomocysteinaemia
 - Valvular heart disease
 - Atrial fibrillation
 - Dyslipoproteinaemia
 - Systemic lupus erythematosus

Women should be advised not to smoke if they wish to use a CHC. Women over 35 years who continue to smoke should be strongly advised to use a different method of contraception.

If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.

The user group of Diane-35 ED is likely to include patients that may have an inherently increased cardiovascular risk.

Symptoms of ATE

Women should be informed of the symptoms of ATE and be advised to seek urgent medical attention if ATE symptoms develop and to inform the healthcare professional that she is taking a CHC.

Symptoms of stroke can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body
- sudden trouble walking, dizziness, loss of balance or coordination
- sudden confusion, slurred speech or aphasia; sudden partial or complete loss of vision; diplopia
- sudden, severe or prolonged headache with no known cause
- loss of consciousness or fainting with or without seizure

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

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
- feeling of being full, having indigestion or choking
- sweating, nausea, vomiting or dizziness

- extreme weakness, anxiety, or shortness of breath
- rapid or irregular heartbeats

Tumours

The most important risk factor for cervical cancer is persistent human papillomavirus (HPV) infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g. cervical screening and sexual behaviour including use of barrier contraceptives.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently taking COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

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

Other Conditions

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when taking COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. A relationship between COC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the doctor to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis, and otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in women with diabetes taking low-dose COCs (containing < 50 µg ethinylloestradiol). However, women with diabetes should be carefully observed while taking COCs.

Crohn's disease and ulcerative colitis have been associated with COC use.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

If in women suffering from hirsutism, symptoms have recently developed or increased substantially, the causes (androgen-producing tumour, adrenal enzyme defect) must be clarified by differential diagnosis.

Each beige active tablet contains 31.12 mg of lactose and each white placebo tablet contains 48.25 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose free diet should take this amount into consideration.

Medical Examination/Consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstatement of DIANE-35 ED, guided by the CONTRAINDICATIONS and PRECAUTIONS, and should be repeated periodically. In general, an annual examination is recommended. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests.

Sexually Transmitted Infections (STIs) including Human Immunodeficiency Virus (HIV) infections and AIDS

DIANE-35 ED does not protect against STIs, including HIV infections (AIDS). The woman should be advised that additional barrier contraceptive measures are needed to prevent transmission of STIs.

Reduced Efficacy

The contraceptive efficacy of DIANE-35 ED may be reduced in the event of missed beige active tablets (see DOSAGE AND ADMINISTRATION – Management of missed tablets), vomiting, or diarrhoea during beige active tablet taking (see DOSAGE AND ADMINISTRATION – Advice in gastrointestinal disturbances) or concomitant medication (see INTERACTIONS WITH OTHER MEDICINES).

Reduced Cycle Control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women, withdrawal bleeding may not occur during the placebo tablet interval. If the

COC has been taken according to the directions, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions (see DOSAGE AND ADMINISTRATION) prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

Use in Pregnancy

Pregnancy Category B3¹

Animal studies showed that the drug combination of ethinylloestradiol and cyproterone acetate or cyproterone acetate alone (given at high doses) can cause signs of feminisation in male fetuses if given during the phase of differentiation of the fetal male genital organs. The relevance of these findings to man is not known. Isolated cases of inadvertent use of DIANE-35 ED during pregnancy have so far given no indications of a corresponding risk in humans. Despite this, the possibility must be considered that the use of DIANE-35 ED during the hormone-sensitive phase of differentiation of the genital organs in male fetuses (from about the 45th day of pregnancy) might cause signs of feminisation. For this reason, DIANE-35 ED is contraindicated during pregnancy.

If pregnancy occurs during treatment with DIANE-35 ED, further intake must be stopped.

¹ **Category B3**

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Use in Lactation

The use of DIANE-35 ED is contraindicated during lactation as small amounts of cyproterone acetate are excreted in breast milk. Oestrogen containing oral contraceptives may decrease the quantity and quality of breast milk.

Paediatric use

DIANE-35 ED is only indicated after menarche.

Use in the Elderly

DIANE-35 ED is not indicated after menopause.

Patients with Hepatic Impairment

DIANE-35 ED is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal (see CONTRAINDICATIONS).

Patients with Renal Impairment

DIANE-35 ED has not been specifically studied in renally impaired patients.

Carcinogenicity

Long-term continuous administration of natural and synthetic oestrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver.

In a long-term carcinogenicity study of CPA in rats, an increased incidence of hepatomas was reported at oral dose levels of 50 mg/kg CPA and above. In mouse (and a second rat) carcinogenicity studies, increases in benign proliferative changes (nodular hyperplasia) in liver cells of female mice and male and female rats were reported at oral doses of 2 mg/kg. Because of shortcomings in these studies (inadequate pharmacokinetic data and the need to reassess the liver pathology), the carcinogenic potential of CPA in animals could not be determined.

The clinical relevance of these findings is presently uncertain. Clinical experience and limited epidemiological data available to date do not appear to have supported an increased incidence of hepatic tumours in humans at the recommended clinical dose of 2 mg/day cyproterone acetate. It should also be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumours.

Genotoxicity

There is limited evidence available in the literature suggesting that oestrogens may be weakly genotoxic at high doses. Ethinyloestradiol was negative in studies for DNA-adduct formation in cultured human liver slices and in assays for gene mutations (bacterial or mammalian cells *in vitro*) and gave equivocal results in assays for chromosomal damage (clastogenic effects were not consistently seen and occurred at high doses).

Cyproterone acetate was negative in a standard battery of genotoxicity studies. However, further tests showed that CPA was capable of producing DNA adducts in hepatocytes in rats, dogs and monkeys *in vivo* and also in freshly isolated rat and human liver cells *in vitro* following metabolism by hydroxysteroid sulfotransferases. This DNA adduct formation occurred at exposures that might be expected to occur with the recommended dose regimen for DIANE-35 ED.

CPA increased DNA repair activity in rat and human hepatocytes *in vitro*. CPA was clastogenic in a female rat liver micronucleus test. Other *in vivo* consequences of CPA treatment were an increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats, and an increase of mutation frequency in transgenic rats carrying a bacterial gene as a target for mutations. In all of these positives *in vivo* tests, hepatocyte proliferation is likely to have contributed to the results being positive. CPA had mitogenic activity towards rat hepatocytes *in vitro*, but not human hepatocytes.

Effect on Laboratory tests

The use of preparations like DIANE-35 ED may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

INTERACTIONS WITH OTHER MEDICINES

Effects of other medicines on DIANE-35 ED

Interactions can occur with medicines that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

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.

Women prescribed any of these medicines should temporarily use a barrier method in addition to DIANE-35 ED or choose another method of contraception. The barrier method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the beige active tablets in the DIANE-35 ED pack, the white placebo tablets should be omitted and the next pack be started.

- **Substances increasing the clearance of DIANE-35 ED (diminished efficacy of DIANE-35 ED by enzyme-induction), e.g:**

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John's Wort (*Hypericum perforatum*).

- **Substances with variable effects on the clearance of DIANE-35 ED**

When co-administered with COCs, many HIV/ hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentration of oestrogen or progestogen. These changes may be clinically relevant in some cases.

- **Substances decreasing the clearance of COCs (enzyme inhibitors)**

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

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 35 µg ethinylestradiol.

Influence of DIANE-35 ED on other Medication

Oestrogen/progestogen preparations like DIANE-35 ED may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

In clinical studies, administration of a 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).

Pharmacodynamic interactions

Co-administration of ethinylestradiol-containing medicinal products with direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these has been shown to be associated with increases in alanine aminotransferase (ALT) levels to greater than 20 times the upper limit of normal in healthy female subjects and HCV infected women (see CONTRAINDICATIONS).

Note: The product information of concomitant medications should be consulted to identify potential interactions.

ADVERSE EFFECTS

Various adverse reactions have been associated with oral contraceptive use. The most serious reactions associated with the use of oral contraceptives are discussed under PRECAUTIONS.

The most commonly reported adverse reactions with DIANE-35 ED are nausea, abdominal pain,

increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. They occur in $\geq 1\%$ of users.

Serious adverse reaction is thromboembolism.

In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide on whether its use should be discontinued.

System Organ Class	Common ($\geq 1/100$ to $<1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $\leq 1/1,000$)
Gastrointestinal disorders	Nausea, Abdominal	Vomiting, Diarrhoe	
Metabolism and nutrition disorders		Fluid retention	
Psychiatric disorders	Depressed mood, Altered mood	Decreased libido	Increased libido
Nervous system disorders	Headache	Migraine	
Skin and subcutaneous tissue disorders		Rash, Urticaria	Erythema nodosum, Erythema multiforme
Eye disorders			Contact lens intolerance
Reproductive system and breast disorders	Breast pain, Breast tenderness	Breast hypertrophy	Vaginal discharge, Breast discharge
Immune system disorders			Hypersensitivity
Investigations	Increased weight		Decreased weight
Vascular Disorders			Thromboembolism

Other adverse reactions:

Eyes disorders: cataract.

DOSAGE AND ADMINISTRATION

Combined oral contraceptives, when taken correctly have a failure rate of approximately 1% per year.

DIANE-35 ED is to be taken regularly in order to achieve therapeutic efficacy and the required contraceptive protection. Previously used hormonal contraception should be discontinued. The dose regimen of DIANE-35 ED is similar to the usual regimen of most of the COCs. Thus, the same administration rules must be considered. The irregular intake of DIANE-35 ED can lead to intermenstrual bleeding and could deteriorate the therapeutic and contraceptive reliability. Therapy should not be initiated unless pregnancy has been excluded.

Duration of Treatment

Treatment will probably need to be continued for about 6 months and probably much longer to gain an acceptable therapeutic effect, especially if DIANE-35 ED is being used for the treatment of excessive hair. The length of use depends on the severity of the symptoms of

androgenisation and their response to treatment. Acne and seborrhoea usually respond sooner than hirsutism. The need to continue treatment should be evaluated periodically by the treating doctor. It is possible that the original condition will recur once treatment with DIANE-35 ED is stopped.

DIANE-35 ED should be withdrawn 3 to 4 cycles after the treated condition has completely resolved. Repeat course of DIANE-35 ED may be given if the androgen-dependent condition(s) recur. In case of a restart with DIANE-35 ED (following a 4 week or greater tablet-free interval), the increased risk of VTE should be considered (see PRECAUTIONS).

How to take DIANE-35 ED

One tablet is to be taken daily. The tablets must be taken in the order directed on the pack at about the same time every day, with some liquid as needed. Tablet taking should be continuous for 28 consecutive days, starting with a tablet corresponding to that day of the week from the red section of the DIANE-35 ED pack.

If a woman starts on a Monday, Tuesday, Wednesday, Thursday or Friday, her first tablet is a white placebo tablet, while if she starts on a Saturday or Sunday her first tablet will be a beige active tablet. Thereafter, one tablet is taken daily, following the arrows marked on the pack, until all tablets have been taken. Each subsequent pack is started the day after the last tablet of the previous pack.

Withdrawal bleeding should usually occur on day 2 to 3 after the last beige active tablet is taken and may not have finished before the next pack is started.

How to start DIANE-35 ED

- **No preceding hormonal contraceptive use (in the past month)**

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Additional non-hormonal contraceptive methods must be used for the first 14 days of tablet-taking.

- **Changing from a combined hormonal contraceptive (combined oral contraceptive/ COC), vaginal ring**

The woman should start with DIANE-35 ED on the day after the last active tablet of her previous COC.

In case a vaginal ring has been used, the woman should start taking DIANE-35 ED on the day of removal.

- **Changing from a progestogen-only-method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)**

The woman may switch from the minipill on any day, from an implant or the IUS on the day of its removal, or from an injectable when the next injection would be due, but in all of these cases she should be advised to additionally use a non-hormonal method of contraception for the first 14 days of tablet-taking.

- **Following first trimester abortion**

The woman may start immediately. Additional non-hormonal contraceptive methods are necessary for the first 14 days of tablet-taking.

- **After childbirth or a second trimester abortion**

Women should be advised to start 21 to 28 days after delivery or second-trimester abortion. Additional non-hormonal contraceptive methods are necessary for the first 14 days of tablet-taking. If intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

DIANE-35 ED should not be used in breastfeeding women (see PRECAUTIONS (Use in Lactation)).

Additional Contraceptive Precautions

When additional contraceptive precautions are required, the woman should be advised either to abstain from sex, or to use a barrier method of contraception, such as a cap (or diaphragm) plus spermicide, or for her partner to use a condom. Rhythm methods should not be advised as the pill disrupts the cyclical changes associated with the natural menstrual cycle e.g. changes in temperature and cervical mucus.

How to Manage Reduced Reliability

When DIANE-35 ED is taken according to the directions for use, the occurrence of pregnancy is highly unlikely. However, the reliability of contraceptive protection may be reduced under the following circumstances:

- **Management of missed tablets**

Missed white pills from the last row of the blister are placebo (inactive, hormone-free) tablets and thus can be disregarded. However they should be discarded to avoid unintentionally prolonging the placebo tablet phase. **The following advice only refers to missed beige active tablets (rows 1-3 of the blister):**

If the woman is **less than 12 hours** late in taking any beige active tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If the woman is **more than 12 hours** late in taking any beige active tablet, contraceptive protection may be reduced. The more tablets are missed and the closer they are to the regular placebo tablet interval, the higher the risk of a pregnancy.

The management of missed tablets can be guided by the following two basic rules:

1. 'Active tablet'-taking must never be discontinued for longer than 7 days.
2. Seven days of uninterrupted 'active tablet'-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

- **Week 1 of active tablets**

The woman should take the last missed beige active tablet as soon as she remembers, even if this means taking two beige active tablets in one day at the same time, and then continue to take tablets at her usual time. Additional contraceptive precautions should be taken for the next 7 days.

If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered.

- **Week 2 of active tablets**

The woman should take the last missed beige active tablet as soon as she remembers, even if this means taking two beige active tablets at the same time. She then continues to take tablets at her usual time, provided that the woman has taken her tablets correctly in the 7 days preceding the first missed beige active tablet. There is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than one beige active tablet, the woman should be advised to use extra precautions for 7 days.

- **Week 3 of active tablets**

The risk of reduced reliability is imminent because of the forthcoming white placebo tablet interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed beige active tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options and to use extra precautions for the next 7 days as well.

1. The woman should take the last beige active missed tablet as soon as she remembers, even if this means taking two beige active tablets at the same time. She then continues to take tablets at her usual time until the beige active tablets are taken. The 7 white placebo tablets must be discarded. The next pack must be started right away. The woman is unlikely to have a withdrawal bleed until the end of the active tablets of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.
2. The woman may also be advised to discontinue tablet taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the placebo tablet interval, the possibility of a pregnancy should be considered.

- **Advice in case of gastrointestinal disturbances**

In case of severe gastro-intestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3-4 hours after taking a beige active tablet, the advice concerning management of missed tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she should take the extra tablet(s) needed from another pack.

OVERDOSAGE

There have been no reports of serious deleterious effects from overdose. On the basis of general experience with COCs, symptoms that may occur in case of overdose of beige active tablets are: nausea, vomiting and withdrawal bleeding. Withdrawal bleeding may even occur in girls before menarche, if they have accidentally taken DIANE-35 ED. There are no antidotes and further treatment should be symptomatic.

In cases of overdose, it is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdose.

PRESENTATION AND STORAGE CONDITIONS

DIANE-35 ED tablets are contained in blister packs. Each blister contains 21 round beige active tablets containing ethinylloestradiol 35 µg and cyproterone acetate 2 mg, followed by 7 round white placebo tablets.

Carton containing blister packs of 1 x 28 and 3 x 28 tablets. Not all pack sizes may be marketed.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Ltd. ABN
22 000 138 714
875 Pacific Highway
Pymble NSW 2073

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE ARTG

22 July 1992

DATE OF MOST RECENT AMENDMENT

5 January 2018

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REFERENCES:

1. Dinger JC, Heinemann LA, Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. *Contracept* 2007; 75:344-54.
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