

DIANE® 35 ED

Cyproterone Acetate/Ethinylestradiol Tablets

Presentation

DIANE-35 ED: Each memo-pack contains 21 beige active tablets, diameter 5.7mm, containing 2 mg cyproterone acetate and 0.035 mg ethinylestradiol and in addition, 7 larger white placebo tablets diameter 6.8 mm.

All tablets have a lustrous sugar coating.

Uses

Actions

The pilosebaceous unit comprises the sebaceous gland and the hair follicle and is an androgen-sensitive skin component. Acne, seborrhoea, hirsutism and androgenic alopecia are clinical conditions which result from aberrations of this target organ. The clinical conditions may be caused by either an increased sensitivity to or by higher plasma levels of androgen. Both the substances contained in DIANE-35 ED beneficially influence the hyperandrogenic state. Cyproterone acetate is a competitive antagonist on the androgen receptor, has inhibitory effects on the androgen-synthesis in target cells and produces a decrease on the androgen blood concentration through an anti-gonadotropic effect. This anti-gonadotropic effect is amplified by ethinylestradiol which also up-regulates the synthesis of Sex-Hormone-Binding-Globulin (SHBG) in plasma. By this mechanism, it reduces free, biologically available androgen in the circulation.

Treatment with DIANE-35 ED 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 seborrhoea likewise diminishes. In women experiencing mild forms of hirsutism and in particular, slightly increased facial hair, results do not, however become apparent until after several months of use.

The contraceptive effect of DIANE-35 ED is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion. As well as protection against pregnancy, oestrogen/progestogen combinations have several positive properties which, next to the negative properties, can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency.

Apart from this, with the higher-dosed combined oral contraceptives (COCs) containing 50 mcg ethinylestradiol, there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. This may also apply to lower-dosed COCs.

Pharmacokinetics

- **Cyproterone acetate**

Absorption

Orally administered cyproterone acetate is rapidly and completely absorbed. Peak serum concentrations of 15 ng/mL are reached at about 1.6 hours after ingestion of a single tablet. Bioavailability is approximately 88%.

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 approximately 986 ± 437 L.

Metabolism

Cyproterone acetate is almost completely metabolised. The main metabolite in plasma was identified as 15beta-OH-CPA which is formed via the cytochrome P450 enzyme CYP3A4. The clearance rate from serum is about 3.6mL/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 – 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 approximately 1.8 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 completely absorbed. Peak serum concentrations of approximately 71 pg/mL are reached at 1.6 hours. During absorption and first-liver passage, ethinylestradiol is metabolised extensively, resulting in a mean oral bioavailability of approximately 45% with a large interindividual variation of approximately 20-65%.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98%) and induces an increase in the serum concentrations of

SHBG. An apparent volume of distribution of about 2.8 – 8.6 L/kg was determined.

Metabolism

Ethinylestradiol is subject to pre-systemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol 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 sulphate. The clearance rate was reported to be approximately 2.3-7 mL/min/kg.

Elimination

Ethinylestradiol serum levels decrease in two disposition phases characterised by half-lives of about 1 h and 10-20 h, respectively. Unchanged drug is not excreted. Ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is approximately 1 day.

Steady-state conditions

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.

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.

Dosage and Administration

DIANE-35 ED is to be taken regularly in order to achieve the 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 combined oral contraceptives. Thus, the same administration rules must be considered. Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year.

The irregular intake of DIANE-35 ED can lead to intermenstrual bleeding and could deteriorate the therapeutic and contraceptive reliability.

How to take DIANE-35 ED

Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. One tablet is to be taken daily. Each subsequent pack is started immediately following 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). The first tablet should be selected from the red starting section of the pack.

Starting on days 2-5 of the menstrual cycle is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

- Changing from another Combined Oral Contraceptive (COC), vaginal ring, or transdermal patch

The woman should start DIANE-35 ED in the red section on the day after the last active tablet of her previous COC, but at the latest on the day following the usual placebo tablet interval of her COC.

In case a vaginal ring or transdermal patch has been used, the woman should start taking DIANE-35 ED preferably on the day of removal, but at the latest when the next application would have been due.

- Changing from a Progestogen-only-method (Minipill, Injection, Implant) or from a progestogen-releasing intrauterine system (IUS)

The woman may switch any day from the minipill, an implant, IUS on the day of its removal or from an injectable when the next injection would be due, but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

- Following First-Trimester Abortion

The woman may start tablet-taking immediately. When doing so, she need not take additional contraceptive measures.

- Following Delivery or Second-Trimester Abortion

Women should be advised to start on day 21 to 28 after delivery or second-trimester abortion.

When starting later than day 28, the woman should be advised to additionally use a barrier method for the first 7 days of tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of DIANE-35ED use or the woman has to wait for her first menstrual period.

For breast-feeding woman- see Use in Lactation.

Management of Missed Tablets

Errors in taking the white placebo tablets contained in DIANE-35 ED can be ignored. 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 user 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 user is **more than 12 hours** late in taking any beige active tablet, contraceptive protection may be reduced.

There is a particularly high risk of pregnancy if tablets are missed at the beginning or end of the week of the white placebo tablets. If tablets are missed in the first week of taking active tablets and intercourse took place in the preceding 7 days the possibility of pregnancy should be considered.

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

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

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

These rules form the basis of the instructions to patients provided in the package insert.

Extra Contraceptive Precautions

When you need extra contraceptive precautions, either:

- don't have sex; or
- use a cap plus spermicide; or
- use a condom

Do not use the rhythm or temperature methods as extra contraceptive precautions. This is because oral contraceptives alter the usual menstrual cycle changes such as changes in temperature and cervical mucus.

The 7 Day Rule

- Continue taking your pills.
- You will not be protected from pregnancy until you have taken your daily small beige active pill for the next 7 days in a row.
- Use another method of contraception (extra contraceptive precautions) such as condoms or do not have sexual intercourse for the next 7 days while taking the next 7 small beige active pills.
- If there are fewer than 7 small beige active pills left in the pack, finish the small active pills and go straight on to the small beige active pills of the next pack. This means that you miss out the large white placebo pills in the 28-day pack. You may not have a period until the end of the next pack. This is not harmful.

Advice in Case of Gastrointestinal Disturbances

In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken. The advice concerning missed tablets should be followed.

If vomiting occurs within 3-4 hours after tablet taking, absorption may not be complete. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra active tablet(s) needed from another pack.

How to Shift Periods or How to Delay a Period

To delay a period the woman should continue with active tablets from another pack of DIANE-35 ED without taking the white placebo tablets. The extension can be carried on for as long as desired until the end of the second pack. During the extension the woman may experience breakthrough bleeding or spotting.

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming tablet-free interval or omit the white placebo tablets in DIANE-35ED by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the second pack (just as when delaying a period).

Length of Use

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. 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 of DIANE-35 ED (following a 4 week or greater pill free interval), the increased risk of VTE should be considered (see Warnings and Precautions).

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 a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction), or of a cerebrovascular accident
- Presence or history of prodromi of a thrombosis (e.g. transient ischemic attack, angina pectoris)
- History of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see Warnings and Precautions)
- Severe hepatic disease as long as liver function values have not returned to normal
- 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)
- 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.

Warnings and Precautions

The clinical and epidemiological experience with oestrogen/progestogen combinations like DIANE-35 ED is predominantly based on combined oral contraceptives (COC). Therefore, the following warnings related to the use of COC apply also for DIANE-35 ED.

If any of the conditions/risk factors mentioned below are present, the benefits of the use 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 on whether use of DIANE-35 ED should be discontinued.

- **Circulatory Disorders**

Epidemiological studies have suggested an association between the use of COCs 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.

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs. The risk for venous thromboembolism is highest during the first year a woman takes a COC. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

This study has shown that the frequency of VTE diagnosis range from 8 to 10 per 10,000 woman years in low oestrogen dose (< 50 µg ethinyloestradiol) COC users. The most recent data suggest that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman years in non-pregnant non-COC users, and range from 20 to 30 per 10,000 pregnant women or post partum.

Overall the risk of VTE in users of low oestrogen dose (< 50 µg ethinyloestradiol) COCs is 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.

VTE may be fatal (in 1-2% of the cases).

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

users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

Symptoms of venous (includes pulmonary embolism (PE) and deep venous thrombosis (DVT)) or arterial thrombotic/thromboembolic (includes myocardial infarction (MI), vascular occlusion and cerebrovascular accident) events can include: unilateral leg pain and/or swelling; 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; sudden severe pain in the chest which may increase with deep breathing, 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; rapid or irregular heartbeat; sudden onset of unexplained shortness of breath or rapid breathing; sudden onset of coughing which may bring up blood; sudden, severe prolonged headache with no known cause; sudden partial or complete loss of vision; diplopia; sense of anxiety; dizziness; slurred speech or aphasia; sudden confusion; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; "acute" abdomen; fullness, indigestion or choking feeling; sweating; nausea; vomiting.

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).

Arterial thromboembolic events may be fatal.

The risk of thromboembolism (venous and/or arterial) or of a cerebrovascular accident increases with:

- Age
- Smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
- A positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any COC use
- Obesity (body mass index over 30 kg/m²)
- Dyslipoproteinemia
- Hypertension
- Migraine
- Valvular heart disease
- Atrial fibrillation

- Prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

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

The increased risk of thromboembolism in the puerperium must be considered.

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, polycystic ovary syndrome, systemic lupus erythematosus, haemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

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

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

When considering risk/benefit, the doctor 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 COCs (< 0.05mg ethinylloestradiol) use.

- **Tumours**

The most important risk factor for cervical cancer is persistent 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.

- **Other Conditions**

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

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. 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; 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 diabetics taking COCs. However, diabetic women 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.

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 warnings. This should be repeated periodically during the use of DIANE-35 ED. 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 DIANE-35 ED. 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 Diseases including HIV infections and AIDS**

Women should be advised that preparations like DIANE-35 ED do not protect against HIV infections (AIDS) and other sexually transmissible diseases (STDs). The woman should be advised that additional barrier contraceptive measures are needed to prevent transmission of STDs.

- **Reduced Efficacy**

The efficacy of DIANE-35 ED may be reduced in the event of missed beige active tablets, vomiting or diarrhoea during active tablet-taking or concomitant medication (see Dosage and Administration).

- **Reduced Cycle Control**

With oestrogen/progestogen combinations, 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 tablet-free 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 prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

Pregnancy and Lactation

Use in Pregnancy

The administration of DIANE-35 ED is contraindicated during pregnancy.

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

Use in Lactation

The administration of DIANE-35 ED is also contraindicated during lactation. Cyproterone acetate is transferred into the milk of lactating women. About 0.2% of the maternal dose will reach the newborn via milk corresponding to a dose of about 1 mcg/kg. During established lactation 0.02 % of the daily maternal dose of ethinyloestradiol could be transferred to the newborn via milk.

Children and adolescents

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.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of COCs.

Preclinical Safety Data

- Ethinyloestradiol

The toxicity profile of ethinyloestradiol is well known. There are no preclinical data of relevance to the prescriber that provide additional safety information to those already included in other sections of the product information.

- Cyproterone acetate

Preclinical data reveal no specific risk for humans based on conventional studies of repeated dose toxicity.

No animal-experimental studies into a possible sensitising effect of ethinyloestradiol and cyproterone acetate have been carried out.

- Embryotoxicity/Teratogenicity

Investigations into embryotoxic or teratogenic effects, using the combination of the two active ingredients, showed no effects indicative of a general teratogenic effect following treatment during organogenesis before development of the external genital organs. Administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs (after approx. day 45 of pregnancy) could lead to signs of feminisation

in male foetuses following higher doses. Observation of male newborn children who had been exposed *in utero* to cyproterone acetate did not show any signs of feminisation. However, pregnancy is a contraindication for the use of DIANE-35 ED.

- Genotoxicity and Carcinogenicity

Recognised 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, whereas the DNA-adduct level in dog liver cells was extremely low.

This DNA-adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. *In vivo* consequences of cyproterone acetate treatment were the 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 target for mutations.

Clinical experience and well conducted epidemiological trials to-date would not support an increased incidence of hepatic tumours in man. Nor did investigations into the tumourigenicity of cyproterone acetate in rodents reveal any indication of a specific tumourigenic potential. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

On the whole, the available findings do not raise any objection to the use of DIANE-35 ED in humans if used in accordance with the directions for the given indication and at the recommended dose.

Adverse Effects

The most serious undesirable effects associated with the use of COCs such as DIANE-35 ED have been referred to in the Warnings and Precautions section. These include venous and arterial thromboembolic disorders.

Other side effects that have been reported in users of DIANE-35 ED but for which the association has been neither confirmed nor refuted are:

System Organ Class	Common (≥ 1/100)	Uncommon (≥ 1/1,000 and < 1/100)	Rare (<1/1,000)
Eye disorders			Contact lens intolerance
Gastrointestinal disorders	Nausea, Abdominal pain	Vomiting, Diarrhoea	
Immune system			Hypersensitivity

disorders			
Investigations	Increased weight		Decreased weight
Metabolism and nutrition disorders		Fluid retention	
Nervous system disorders	Headache	Migraine	
Psychiatric disorders	Depressed mood, Altered mood	Decreased libido	Increased libido
Reproductive system and breast disorders	Breast pain, Breast tenderness	Breast hypertrophy	Vaginal discharge, Breast discharge
Skin and subcutaneous tissue disorders		Rash, Urticaria	Erythema nodosum, Erythema multiforme

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

Interactions

Interactions between oestrogen/progestogen combinations like DIANE-35 ED and other drugs may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

Substances diminishing the efficacy of COCs (enzyme inducers and antibiotics)

- *Enzyme induction (increase of hepatic metabolism):*

Interactions can occur with medicines that induce microsomal enzymes (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifabutin, rifampicin and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John's Wort (*Hypericum perforatum*)) which can result in increased clearance of sex hormones.

HIV protease (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and combinations of them, have been reported to potentially affect hepatic metabolism.

Women prescribed any of these medicines should temporarily use a barrier method in addition to DIANE-35 ED or choose another method of contraception. With microsomal enzyme-inducing medicines, the barrier

method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

- *Antibiotics (interference with Enterohepatic Circulation):*

Some clinical reports suggest that entero hepatic circulation of oestrogens may decrease when certain antibiotic agents are given, which may reduce ethinyloestradiol concentrations (e.g. penicillins, tetracyclines).

Women prescribed antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after completing a course of antibiotics. If the period in which the barrier method is used includes the white placebo tablets, they should not be taken and the next pack started without delay.

- *Influence of DIANE-35 ED on other medication*

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

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

- **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 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.

Overdosage

There have been no reports of serious deleterious effects from overdose.

Symptoms

Symptoms that may occur in this case are nausea, vomiting and, in young girls, slight vaginal bleeding.

Treatment

There are no antidotes and further treatment should be symptomatic.

Pharmaceutical Precautions

Shelf Life: 5 years

Special Precautions for Storage: Store below 30°C

Medicine Classification

Prescription Medicine

Package Quantities

3 calendar-packs containing 28 tablets.

DIANE-35 ED tablets are contained in blister packs consisting of deep-drawn strips made of polyvinyl chloride film with counter sealing foil made of aluminum with heat sealable coating.

Further Information

List of Excipients

Lactose monohydrate, maize starch, povidone, magnesium stearate, sucrose, macrogol 6000, calcium carbonate, purified talc, glycerol, titanium dioxide, iron oxide yellow, glycol montanate.

Instructions for Use/Handling

Store all drugs properly and keep them out of reach of children.

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Date of Preparation

13 October 2011