Diane® 35

Coated Tablet

1. NAME OF THE MEDICINAL PRODUCT

Diane-35 0.035 mg / 2.0 mg coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

21 hormone-containing beige coated tablets:
Each coated tablet contains 0.035 mg ethinylestradiol, 2.0 mg cyproterone acetate

3. PHARMACEUTICAL FORM

Coated tablet

4. CLINICAL PARTICULARS

4.1 Indication

Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age. This includes patients with polycystic ovary syndrome requiring treatment of these symptoms.

For the treatment of acne, Diane-35 should only be used after topical therapy or systemic antibiotic treatments have failed.

Since Diane-35 is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives (see section 'Contraindications').

4.2 Dosage and method of administration

Note: DIANE-35 should not be prescribed for the purpose of contraception alone. However, when taken as recommended, 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.

Method of administration
Oral use

Dosage regimen
How to take Diane-35
Diane-35 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 is similar to the usual regimen of most of the 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 can lead to intermenstrual bleedings and could deteriorate the therapeutic and contraceptive reliability.

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 for 21 consecutive days. Each subsequent pack is started after a 7-day tablet-free interval, during which time a withdrawal bleed usually occurs. This usually starts on day 2-3 after the last coated tablet and may not have finished before the next pack is started.

How to start Diane-35
► *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). Starting on days 2-5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

► *Changing from a combined hormonal contraceptive (combined oral contraceptive /COC), vaginal ring, or transdermal patch*

The woman should start with Diane-35 preferably on the day after the last hormone-containing tablet of her previous COC, but at the latest on the day following the usual tablet-free or hormone-free tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Diane-35 preferably on the day of removal of the last ring or patch of a cycle pack, 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 (from an implant or the IUS on the day of its removal, 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 immediately. When doing so, she does not need additional contraceptive measures.

► *Following delivery or second-trimester abortion*

For breastfeeding women see section 'Pregnancy and lactation'

Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, 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-35 use or the woman has to wait for her first menstrual period.

Management of missed tablets

If the user is **less than 12 hours** late in taking any 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 she is **more than 12 hours** late in taking any tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. tablet-taking must never be discontinued for longer than 7 days.
2. 7 days of uninterrupted 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*

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the regular tablet-free interval, the higher the risk of a pregnancy.

► *Week 2*

The user should take the last missed tablet as soon as she remembers, even if this means taking two 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 tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

► *Week 3*

The risk of reduced reliability is imminent because of the forthcoming tablet-free 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 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 user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next pack must be started as soon as the current pack is finished, i.e., no gap should be left between packs. The user is unlikely to have a withdrawal bleed until the end 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 first normal tablet-free interval, the possibility of a pregnancy should be considered.

Advice in case of gastro-intestinal 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 tablet-taking, the advice concerning missed tablets, as given in section 'Management of missed tablets', is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

Length of use
The length of use depends on the severity of the symptoms of androgenization and their response to treatment. In general, treatment should be carried out over several months. Time to relieve of symptoms is at least three months. Acne and seborrhea usually respond sooner than hirsutism The need to continue treatment should be evaluated periodically by the treating physician.

Should there be a recurrence of symptoms, weeks or months after discontinuation of tablet taking, treatment with Diane 35 may be resumed. In case of a restart of Diane-35 (following a 4 week or greater pill free interval), the increased risk of VTE should be considered (see section 'Special warnings and precautions for use').

Additional information on special populations
*Pediatric patients*Diane-35 is only indicated after menarche.

Geriatric patients
Not applicable. Diane-35 is not indicated after menopause.

Patients with 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'.

Patients with 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.

4.3 Contraindications

Preparations containing estrogen/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 a history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- ► A high risk of venous or arterial thrombosis (see 'Special warnings and precautions for use').
- ► History of migraine with focal neurological symptoms.
- ► Diabetes mellitus with vascular involvement.
- ► Severe hepatic disease as long as liver function values have not returned to normal.
- ► Diane is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir (See Section Warnings and Precautions and Section Interactions with Other Medicaments).
- ► Presence or history of liver tumors (benign or malignant).
- ► Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- ► Undiagnosed vaginal bleeding.
- ► Concomitant use with another hormonal contraceptive (see section'Indication(s)')
- ► Known or suspected pregnancy.
- ► Lactation
- ► Hypersensitivity to the active substances or to any of the excipients.

Diane-35 is not for use in men.

4.4 Special warnings and precautions for use

Diane-35 is composed of the progestogen cyproterone acetate and the estrogen ethinylestradiol and is administered for 21 days of a monthly cycle. It has a similar composition to that of a combined oral contraceptive (COC). The clinical and epidemiological experience with estrogen/progestogen combinations like Diane 35 is predominantly based on combined oral contraceptives (COC). Therefore, the following warnings related to the use of COC apply also for Diane-35.

Warnings
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.

The risk of VTE is highest during the first year of use. 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.

Overall the risk for venous thromboembolism (VTE) in users of low estrogen dose (< 50 µg ethinylestradiol) 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 life-threatening or may have a fatal outcome (in 1-2 % of the cases).

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs.

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

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

Symptoms of MI can include: pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.
Arterial thromboembolic events may be life-threatening or may have a fatal outcome.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor.
This increased risk may be greater than a simple cumulative risk of the factors. Diane-35 should not be prescribed in case of a negative risk benefit assessment. (see section ‘Contraindications’)

The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:

- ► age;
- ► obesity (body mass index over 30 kg/m^2);
- ► 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;
- ► prolonged immobilization, 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 remobilization.
- ► smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- ► dyslipoproteinemia;
- ► hypertension;
- ► migraine;
- ► valvular heart disease;
- ► atrial fibrillation;

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 (for information on pregnancy and lactation see section ‘Pregnancy and lactation’).

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 ovary syndrome.

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus , hemolytic 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 Diane-35 use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of Diane-35.

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 COCs (<0.05 mg ethinylestradiol).

Tumors
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 using 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 tumors, and even more rarely, malignant liver tumors have been reported in users of COCs. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. 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 COCs.

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

ALT elevations
During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir with/without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occured significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Patients who are taking ethinylestradiol-containing medicinal products must switch to an alternative method of contraception (e.g. progestin only contraception or non-hormonal methods) prior to initiating ombitasvir / paritaprevir / ritonavir and dasabuvir therapy (See Section Contraindications and Section Interactions with Other Medicaments).

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 physician 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; hemolytic uremic syndrome; Sydenham’s chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens 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 using low-dose COCs (containing < 0.05 mg ethinylestradiol). 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.

Medical examination/consultation
Women should be advised that preparations like Diane-35 do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy
The contraceptive effect of Diane-35 may be reduced in the event of e.g. missed tablets (section 'Management of missed tablets'), gastro-intestinal disturbances (section 'Advice in case of gastro-intestinal disturbances') during tablet taking or concomitant medication (section 'Interaction with other medicinal products and other forms of interaction').

Reduced cycle control
With estrogen/progestogen combinations, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use.

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions described in section 'Dosage and method of administration', 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.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal product on Diane-35
Interactions can occur with drugs 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 on treatment with any of these drugs should temporarily use a barrier method in addition to Diane-35 or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

If the period during which the barrier method is used runs beyond the end of the tablets in the Diane-35 pack, the next pack should be started without the usual tablet-free interval.

Substances increasing the clearance of Diane-35 (diminished efficacy of Diane-35 by enzyme-induction), e.g.:
► *P*henytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort).

Substances with variable effects on the clearance of Diane-35, e.g.:
When co-administered with Diane-35, many HIV/HCV protease inhibitors and nonnucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of Diane-35 (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the estrogen or the progestin 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 0.035 mg ethinylestradiol.

Effects of estrogen/progestogen combinations on other medicinal products
Estrogen/progestogen combinations like Diane-35 may affect the metabolism of certain other drugs. 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 interaction

Concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (See Section Contraindications and Section Warnings and Precautions). Therefore, users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. Diane can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Other forms of interactions
► *Laboratory tests*
The use of preparations like Diane-35 may influence the results of certain laboratory tests.

4.6 Pregnancy and lactation

Pregnancy
Diane-35 is not indicated during pregnancy. If pregnancy occurs during treatment with Diane-35, further intake must be stopped (see section 'Preclinical safety data').

Lactation
The administration of Diane-35 is 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 µg/kg. 0.02 % of the daily maternal dose of ethinylestradiol could be transferred to the newborn via milk during established lactation.

4.7 Undesirable effects

4.7.1 Summary of safety profile
The most commonly reported adverse reactions with Diane-35 are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. They occur in ≥ 1 % of users.
Serious adverse reaction is thromboembolism

4.7.2 Tabulated list of adverse reactions

Side effects that have been reported in users of COCs but for which the association has been neither confirmed nor refuted are:

System Organ Class (MedDRA)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1,000 to <1/100)	Rare (≥1/10,000 to < 1/1,000)
Eye disorders			Contact lens intolerance
Gastrointestinal disorders	Nausea Abdominal pain	Vomiting Diarrhea	
Immune system disorders			Hypersensitivity
Investigations	Weight increased		Weight decreased
Metabolism and nutrition disorders		Fluid retention	
Nervous system disorders	Headache	Migraine	
Psychiatric disorders	Depressed mood Mood altered	Libido decreased	Libido increased
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
Vascular Disorders			Thromboembolism

4.7.3 Description of selected adverse reactions

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of combined oral contraceptives are listed below (see also sections 'Contraindications', 'Special warnings and precautions for use'):

Tumors

- The frequency of diagnosis of breast cancer is very slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown
- Liver tumors (benign and malignant)

Other conditions

• Venous thromboembolic disorders

• Arterial thromboembolic disorders

• Cerebrovascular accidents

• Increased risk of pancreatitis when using COCs (women with hypertriglyceridemia)

• Hypertension

• Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss, cervical cancer

• In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema

• Liver function disturbances

• Changes in glucose tolerance or effect on peripheral insulin resistance

• Crohn's disease, ulcerative colitis

• Chloasma

Interactions

Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with oral contraceptives (see 'Interaction with other medicinal products and other forms of interaction').

4.8 Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea, vomiting and, withdrawal bleeding. The last may even occur in girls before their menarche, if they have accidentally taken the medicinal product. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cyproterone acetate is a competitive antagonist on the androgen receptor, has inhibitory effects on the androgen-synthesis in target cells and produces a decrease of the androgen blood concentration through an antigonadotropic effect. This antigonadotropic effect is amplified by ethinylestradiol which up-regulates as well the synthesis of Sexual-Hormone-Binding-Globulin (SHBG) in plasma. It thereby reduces free, biologically available androgen in the circulation.

5.2 Pharmacokinetic properties

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 single ingestion. Bioavailability is about 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 ethinylestradiol-induced increase in 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 almost completely metabolized. The main metabolite in plasma was identified as 15β-OH-CPA which is formed 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 characterized 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 about 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 about 71 pg/ml are reached at 1.6 hours. During absorption and first-liver passage, ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of about 45% with a large interindividual variation of about 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 presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized 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 clearance rate was reported to be about 2.3 - 7 ml/min/kg.

Elimination
Ethinylestradiol serum levels decrease in two disposition phases characterized by half-lives of about 1 hour and 10 – 20 hours, 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 about 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.

5.3 Preclinical safety data

Ethinyl estradiol
The toxicity profile of ethinyl estradiol 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
Systemic toxicity
Preclinical data reveal no specific risk for humans based on conventional studies of repeated dose toxicity.

Embryotoxicity/teratogenicity
Investigations into embryotoxicity using the combination of the two active ingredients showed no effects indicative of a 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 led to signs of feminization in male fetuses following higher doses. Observation of male newborn children who had been exposed in utero to cyproterone acetate did not show any signs of feminization. However, pregnancy is a contraindication for the use of Diane-35.

Genotoxicity and carcinogenicity
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. 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 tumors in man. Nor did investigations into the tumorigenicity of cyproterone acetate in rodents reveal any indication of a specific tumorigenic potential.

However, it must be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumors.

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

6. PHARMACEUTICAL PARTICULARS

List of excipients
lactose monohydrate
maize starch
povidone 25

magnesium stearate
sucrose
povidone 700 000
macrogol 6000
calcium carbonate precipitated
talc
glycerol 85%
titanium dioxide
ferric oxide pigment yellow
montanglycol wax

Special precautions for storage
Store below 30°C
Store all drugs properly and keep them out of reach of children.

Nature and contents of container
Blister pack containing 21 tablets

Manufactured by
Bayer Weimar GmbH und Co. KG
Dobereinerstrasse 20
D-99427 Weimar, Germany

Date of Revision
26 July 2018