Diane®-35
Sugar coated tablets

Important information, please read carefully!

Composition
Each tablet of Diane-35 contains 2 mg Cyproterone acetate and 0.035 mg Ethinylestradiol

Pharmacological Properties
Pharmacodynamic properties

The substance cyproterone acetate contained in Diane-35 inhibits the influence of the androgens which are also produced by the female organism. It is thus possible to treat diseases the cause of which is either an increased production of androgens or a particular sensitivity to these hormones.

Post Authorization Safety Studies (PASS) have shown that the frequency of VTE diagnosis ranges between 7-10 per 10,000 woman years in low estrogen dose (< 50 µg ethinylestradiol) COC users. The most recent data suggest that the frequency of VTE diagnosis is approximately 4 per 10,000 woman years in non-pregnant non-COC users, and ranges between 20 to 30 per 10,000 pregnant women or post partum.

While Diane-35 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. Treatment with Diane-35 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 sole administration of cyproterone acetate would thus lead to cycle disturbances which are avoided by its combination with ethinylestradiol in Diane-35.

This holds true as long as the preparation is taken cyclically according to the instructions.

The contraceptive effect of Diane-35 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. In addition to protection against pregnancy, estrogen/progestogen combinations have-besides adverse properties (see sections 'Warnings', 'Undesirable effects') - positive properties: 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, there is evidence of reduced risk of endometrial cancer and ovarian cancer. Furthermore, the higher dose COCs (0.05 mg Ethinylestradiol) have been shown to reduce the incidence of ovarian cysts, pelvic inflammatory disease, benign breast disease and ectopic pregnancy. Whether this also applies to lower-dosed COCs remains to be confirmed.

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.

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. No animal experimental studies into a possible sensitizing effect of ethinylestradiol and cyproterone acetate have been carried out.

Embryotoxic/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.

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.

Indications
Treatment of moderate to severe acne related to androgen sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age.

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.

Dosage and method of administration
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 failure rate may increase when pills are missed or taken incorrectly.

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 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 oral contraceptive (COC)*
  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.
- ▶ *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 breast feeding women see 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. 7days 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

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.

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.
- ▶ Sickle-cell anemia
- ▶ Diabetes mellitus with vascular involvement.
- ▶ 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 'Interaction with other medicinal products and other forms of interaction')
- ▶ 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).
- ▶ Concomitant use with another hormonal contraceptive (see section Indications)
- ▶ Undiagnosed vaginal bleeding.
- ▶ Known or suspected pregnancy.
- ▶ Lactation
- ▶ Hypersensitivity to the active substances or to any of the excipients.

Diane-35 is not for use in men.

Special warnings and special 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

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

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

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/m²);
- ▶ 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 ovarian 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, hyserhomocysteinemia, 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.

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 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.

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

Each coated tablet of this medicinal product contains 31 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the 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 reinstitution Diane-35, guided by the contraindications (section 'Contraindications') and warnings (section 'Warnings'), and should be repeated periodically. 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. The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman but should generally include special reference to blood pressure, breast, abdomen and pelvic organs, including cervical cytology.

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. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaption 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 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.

Reasons for stopping Diane-35 immediately:

- ▶ Occurrence for the first time, or exacerbation, of migrainous headaches or unusually frequent or unusually severe headaches.
- ▶ Sudden disturbances of vision or hearing loss or other perceptual disorder.
- ▶ First sign of thrombophlebitis or thromboembolic symptoms (e.g. unusual pains in or swelling of the leg (s), stabbing pains on breathing or coughing for no apparent reason). Feeling of pain and tightness in the chest.
- ▶ Six week before an elective major operation (e.g. abdominal, orthopaedic), any surgery to the legs, medical treatment for varicose veins or prolonged immobilisation, e.g. after accidents or surgery. Do not restart until 2 weeks after full ambulation. In case of emergency surgery, thrombotic prophylaxis usually indicated e.g. subcutaneous heparin.
- ▶ Onset of jaundice, hepatitis, itching of the whole body.
- ▶ Increase in ephileptic seizure.
- ▶ Significant rise in blood pressure.
- ▶ Onset of severe depression.
- ▶ Severe upper abdominal pain or liver enlargement.
- ▶ Clear exacerbation of conditions known to be capable of deteriorating during oral contraception or pregnancy.
- ▶ Pregnancy is a reason for stopping immediately because it has been suggested by some investigations that oral contraceptives taken in early pregnancy may slightly increase the risk of foetal malformations. Other investigations have failed to support these findings. The possibility therefore cannot be excluded, but it is certain that if a risk exists at all, it is very small.

Precautions:

The following conditions require strict medical supervision during medication with oral contraceptives. Deterioration or first appearance of any of these conditions may indicated that Diane-35 should be discontinued.

- ▶ Diabetes mellitus, or a tendency towards diabetes mellitus (e.g. unexplained glycosuria), hypertension, varicose veins, a history of phlebitis, otosclerosis, multiple sclherosis, epilepsy, porphyria, tetany, disturbed liver function, Sydenham's chorea, renal dysfunction, family history of clotting disorder, obesity. Family history of breast cancer and patient history of benign breast disease, history of clinical depression, systemic lupus erythematosus, uterine fibroids, an intolerance of contact lenses, migraine, gall-stones, cardiovascular disease, chloasma, asthma, or any disease that is prone to worsen during pregnancy.
- ▶ It should be borne in mind that the use of ultraviolet lamps, for the treatment of acne, or prolonged exposure to sunlight, increases the risk of the deterioration of chloasma.
- ▶ Some women may experience amenorrhoea or oligomenorrhoea after discontinuation of Diane-35, especially when these conditions existed prior to use. Women should be informed of this possibility

Interaction with other medicinal products and other forms of interaction
Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

Effects of other medicinal products 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.:

Phenytoin, 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 non-nucleoside 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 vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical studies, administration of 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

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 ALT levels to greater than 20 times the upper limit of normal in healthy female subjects and HCV infected women (see 'Contraindications').

Other forms of interactions

- ▶ *Laboratory tests*

The use of preparations like Diane-35 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.

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.

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 Diane-35.

Undesirable effects
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

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 (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)
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

* The most appropriate MedDRA term (version 12.0) to describe a certain adverse reaction is listed.

Synonyms or related conditions are not listed, but should be taken into account as well.

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').

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 accidentally taken the medicinal product. There are no antidotes and further treatment should be symptomatic.

Presentation
Calendar pack containing 21 tablets

Reg. No.: DKI0806820416A1

Instruction for use/handling
Store all drugs properly and keep them out of reach of children.

Do not store above 30°C

Harus dengan resep dokter

Imported by:
PT Bayer Indonesia,
Depok-Indonesia
Manufactured by:
Bayer Weimar GmbH und Co. KG, Weimar-Germany
Packed & released by Bayer AG, Berlin-Germany

Fajar Permatasari
Digitally signed by Fajar Permatasari
Date: 2020.05.12 09:15:08 +07'00'

Anisa Tiffany Yuliani
Digitally signed by Anisa Tiffany Yuliani
Date: 2020.05.13 11:52:43 +07'00'

Pembuatan Terjemahan/Rantai Sistem | Page: 1 | Date: 12.05.2020
Jam: 10:46:00 | Job: 8723 | Size: 297 x 420 mm | Color: 0C,0M,0Y,0K
Office: BLR | Job: 120100 | Operator: Damar Yalinkilic
Technical Document | Format: 595 x 841 mm
Bayer AG, Leverkusen, Germany
Bayer Healthcare
Pharmaceuticals
Damar Yalinkilic
Design Center Berlin
Bayer AG
51368 Leverkusen
Germany
8723.09.01.indd 1 11.05.2020 08:46:54

DISETUJUI OLEH BPOM : 08/03/2021
ID : EREG100366VR12000066

Diane®-35

Tablet salut gula

Informasi penting, bacalah secara seksama!

Komposisi

Setiap tablet Diane-35 mengandung 2 mg Siproteron asetat dan 0,035 mg etinilestradiol.

Sifat Farmakologi

Sifat farmakodinamik

Siproteron asetat yang terdapat dalam Diane-35 menghambat pengaruh androgen yang juga diproduksi wanita sehingga dapat mengatasi penyakit yang disebabkan oleh peningkatan produksi androgen atau sensitivitas tertentu terhadap hormon-hormon ini.

Studi keamanan pasca persetujuan menunjukkan frekuensi kisaran diagnosis VTE antara 7 - 10 dari 10.000 wanita pengguna KOK yang mengandung estrogen dosis rendah (<50 µg etinilestradiol). Sebagian besar data yang tersedia memperlihatkan bahwa frekuensi diagnosis VTE rata-rata sebesar 4 dari 10.000 wanita bukan pengguna KOK dan tidak hamil, and rata-rata antara 20 sampai 30 dari 10.000 wanita hamil dan setelah melahirkan.

Pada saat Diane-35 diminum, peningkatan fungsi kelenjar sebasea yang berperan penting dalam terjadinya jerawat dan seborea akan berkurang. Setelah 3-4 bulan terapi, efficoresi jerawat akan sembuh. Umumnya, kelebihan lemak di jambul dan kulit lebih dulu hilang. Diane-35 diindikasikan untuk wanita usia subur dengan hirsutisme ringan, terutama dengan sedikit peningkatan rambut pada wajah; meskipun demikian, hasilnya baru terlihat setelah digunakan beberapa bulan.

Selain efek antiandrogen, Siproteron asetat juga mempunyai efek progestasional yang nyata. Pemberian Siproteron asetat saja dapat mengganggu siklus haid; hal ini dapat dihindari dengan kombinasinya bersama etinilestradiol dalam Diane-35. Ini berlaku selama obat diminum sesuai petunjuk.

Efek kontrasepsi Diane-35 didasarkan atas interaksi dari berbagai faktor, yang terpenting adalah penghambatan ovulasi dan perubahan-perubahan sekresi leher rahim. Selain mencegah kehamilan, kombinasi estrogen/progestogen selain mempunyai sifat tidak diinginkan (lihat 'Peringatan', 'Efek yang tidak diinginkan') juga mempunyai sifat positif yaitu: siklus haid menjadi lebih teratur dan nyeri menstruasi serta darah haid berkurang. Berkurangnya darah haid menyebabkan berkurangnya defisiensi besi.

Selain itu, risiko kanker endometrium dan kanker ovarium juga berkurang. Dosis KOK (Kontrasepsi Oral Kombinasi) yang lebih tinggi (0,05 mg etinilestradiol) terbukti mengurangi terjadinya kista ovarium, penyakit radang panggul, kehamilan payudara jinak, dan kehamilan ektopik. Apakah hal ini juga berlaku untuk KOK dosis lebih rendah masih perlu dibuktikan.

Sifat farmakokinetik

Siproteron asetat

Absorpsi

Pemberian siproteron asetat oral diserap secara cepat dan lengkap. Kadar serum maksimum 15ng/ml dicapai sekitar 1,6 jam setelah pemberian. Bioavailabilitas sekitar 88%.

Distribusi

Sebagian besar siproteron asetat terikat dengan protein plasma. Hanya 3,5-4% dari total kadar serum obat terdapat sebagai steroid bebas. Peningkatan SHBG yang dipicu etinilestradiol tidak mempengaruhi ikatan serum protein siproteron asetat. Volume distribusi siproteron asetat rata-rata adalah 986±437 l.

Metabolisme

Siproteron asetat hampir secara lengkap dimetabolisme. Metabolit utama didalam plasma berupa 15β-OH-CPA yang dibentuk oleh sitokrom P450 enzim CYP3A4. Kecepatan klirens dari serum sekitar 3,6 ml/min/kg.

Eliminasi

Kadar serum siproteron asetat berkurang dalam dua fase ditandai oleh waktu paruh sekitar 0.8 jam dan 2,3-3,3 hari. Sebagian siproteron asetat diekskresi dalam bentuk utuh. Metabolit-metabolit tersebut diekskresi melalui saluran urin dan empedu dengan rasio sekitar 1:2. Waktu paruh ekskresi metabolit sekitar 1,8 hari.

Kondisi steady-state

Farmakokinetik siproteron asetat tidak dipengaruhi oleh kadar SHBG. Pada pemberian setiap hari kadar serum obat meningkat sekitar 2,5 kali sampai kelipatannya pada kondisi steady-state selama waktu paruh kedua siklus pengobatan.

Etinylestradiol

Absorpsi

Pemberian etinilestradiol secara oral diserap dengan cepat dan lengkap. Kadar serum maksimum sekitar 71 pg/ml dicapai pada 1,6 jam. Selama absorpsi dan metabolisme hati lintas pertama, etinilestradiol dimetabolisme secara ekstensif, dan menghasilkan bioavailabilitas oral rata-rata sekitar 45% dengan besar variasi interindividual sekitar 20-65%.

Distribusi

Etinilestradiol terikat kuat, tetapi tidak spesifik dengan protein plasma (sekitar 98%), dan memicu peningkatan kadar serum SHBG. Volume distribusi rata-rata yang ditentukan sekitar 2,8-8,6 l/kg.

Metabolisme

Etinilestradiol adalah subyek konjugasi presistemik di mukosa usus halus dan hati. Etinilestradiol terutama dimetabolisme oleh hidroksilasi aromatik yang membentuk berbagai jenis metabolit hidroksilasi dan metilasi, umumnya terdapat sebagai metabolit bebas dan sebagai konjugasi dengan glukuronida dan sulfat. Kecepatan klirens sekitar 2,3-7 ml/menit/kg.

Eliminasi

Kadar serum etinilestradiol berkurang dalam dua fase ditandai oleh waktu paruh sekitar 1 jam dan 10-20 jam, berturut-turut. Etinilestradiol tidak diekskresi dalam bentuk utuh. Metabolit etinilestradiol diekskresi melalui saluran urin dan empedu dengan rasio sekitar 4:6. Waktu paruh ekskresi metabolit sekitar 1 hari.

Kondisi steady-state

Kondisi steady-state dicapai dalam paruh kedua dari siklus pengobatan ketika kadar serum obat lebih tinggi sampai 60% dibandingkan pada pemberian dosis tunggal.

Data keamanan preklinis

Etinilestradiol

Profil toksisitas etinilestradiol sudah diketahui dengan baik. Tidak ada data preklinik terkait yang memberikan informasi keamanan tambahan kepada dokter selain yang sudah disebutkan pada bagian informasi produk.

Siproteron asetat

Toksisitas sistemik

Data preklinis menunjukkan tidak ada risiko spesifik pada manusia berdasarkan studi-studi toksisitas dosis berulang konvensional. Tidak pernah dilakukan studi eksperimental pada hewan tentang kemungkinan terjadinya efek sensitivasi etinilestradiol dan siproteron asetat.

Embriotoksisitas/teratogenisitas

Penelitian embriotoksisitas menggunakan kombinasi kedua zat aktif ini tidak memperlihatkan efek teratogenik setelah pengobatan selama organogenesis sebelum perkembangan organ-organ kelamin luar.

Genotoksisitas dan karsinogenisitas

Test genotoksisitas lini pertama yang sudah dikenal pada siproteron asetat memberikan hasil negatif. Tetapi test lebih lanjut menunjukkan bahwa siproteron asetat dapat berikatan pada DNA (dan meningkatkan aktivitas perbaikan DNA) pada sel-sel hati tikus dan kera dan juga hepatosit manusia yang baru dilosolasi, kadar molekul tambahan DNA pada sel hati anjing sangatlah rendah.

Pembentukan molekul tambahan pada DNA tertjadi pada paparan sistemik yang mungkin terjadi pada regimen dosis yang dianjurkan untuk siproteron asetat.

Konsekuensi pengobatan siproteron asetat secara in vivo meningkatkan kejadian fokal, pre-neoplastik, lesi hati dimana enzim-enzim selular berubah pada tikus betina dan peningkatan frekuensi mutasi tikus-tikus transgenik yang membawa gen bakteri sebagai target untuk mutasi.

Pengalaman klinis dan studi-studi epidemiologi yang telah dilakukan hingga saat ini tidak mendukung adanya peningkatan kejadian tumor hati pada manusia. Penelitian tumorigenisitas siproteron asetat pada binatang pengerat juga tidak mengindikasikan adanya potensi tumorigenik secara spesifik.

Tetapi perlu dingat bahwa hormon seks dapat meningkatkan pertumbuhan jaringan dan tumor tertentu yang tergantung pada hormon.

Secara keseluruhan, penemuan ini tidak menambah keberatan terhadap penggunaan Diane-35 pada manusia jika digunakan sesuai petunjuk untuk indikasi dan dosis yang dianjurkan.

Indikasi

Pengobatan jerawat sedang sampai berat yang berhubungan dengan sensitivitas androgen (dengan atau tanpa seborea) dan/atau hirsutisme pada wanita usia reproduktif.

Untuk pengobatan jerawat, Diane-35 hanya dapat digunakan bila terapi topikal atau pengobatan dengan antiobiotik sistemik tidak berhasil.

Diane-35 juga berperan sebagai kontrasepsi hormon, maka penggunaan kombinasi dengan kontrasepsi hormon lainnya tidak diperkenankan.

Dosis dan cara pemberian

Cara pemberian

Secara oral

Aturan dosis

Cara menggunakan Diane-35

Diane-35 diminum secara teratur untuk mencapai efikasi terapetik dan perlindungan kontrasepsi yang diperlukan. Penggunaan kontrasepsi hormonal sebelumnya harus dihentikan. Aturan dosis Diane-35 sama dengan kontrasepsi oral kombinasi pada umumnya. Karena itu, aturan pemakaian yang sama harus dipertimbangkan. Bila diminum secara tepat, angka kegagalan dengan kontrasepsi oral kombinasi sekitar 1% per tahun. Angka kegagalan bisa meningkat jika tablet juga diminum atau tidak diminum dengan semestinya.

Pemakaian Diane-35 yang tidak teratur dapat menyebabkan pendarahan intramenstrual (diantara dua waktu menstruasi) dan dapat memperburuk efikasi terapetik dan reliabilitas kontrasepsi.

Tablet harus diminum setiap hari tanpa henti dalam urutan sesuai dengan petunjuk pada kemasan, pada waktu yang kira-kira sama, dengan air secukupnya. Satu tablet diminum setiap hari selama 21 hari berturut-turut. Kemasan berikutnya diminum setelah interval 7 hari bebas tablet, dimana pada saat itu biasanya terjadi perdarahan menstruasi. Perdarahan lucut biasanya terjadi pada hari ke 2-3 setelah dimulai tablet inert (tidak mengandung zat aktif) dan tidak berhenti sebelum kemasan berikutnya mulai diminum.

Cara memulai Diane-35

- ▶ *Tidak menggunakan kontrasepsi hormonal (dalam bulan sebelumnya)*
  Pemakaian tablet harus dimulai pada hari ke-1 dari siklus alami wanita (hari pertama menstruasi). Mulai pada hari ke 2-5 diperbolehkan, akan tetapi selama siklus pertama dianjurkan menggunakan kontrasepsi metode penghalang sebagai tambahan selama 7 hari pertama minum tablet.
- ▶ *Pindah dari kontrasepsi oral kombinasi (KOK).*
  Diane-35 sebaiknya dimulai pada hari setelah pemakaian tablet mengandung hormon terakhir dari KOK sebelumnya, tetapi selambat-lambatnya pada hari pertama setelah masa bebas tablet atau masa minum tablet bebas hormon dari KOK sebelumnya.
- ▶ *Pindah dari metode progestogen saja (minipil, suntik, implant) atau dari sistem intrauterin (IUS) yang melepaskan progestogen.*
  Pasien dapat berpindah dari metoda minipil kapan saja (pada hari pelepasan alat untuk perpindahan dari implant atau IUS, pada hari penyuntikan berikutnya untuk perpindahan dari suntikan), tetapi sebaiknya untuk semua keadaan tersebut dianjurkan untuk menggunakan kontrasepsi metode penghalang selama 7 hari pertama minum tablet.
- ▶ *Setelah keguguran pada trimester pertama.*
  Pasien boleh segera menggunakan obat ini. Jika hal ini dilakukan dia tidak perlu menggunakan kontrasepsi tambahan.
- ▶ *Setelah melahirkan atau setelah keguguran pada trimester kedua*
  Untuk wanita menyusui, lihat bagian 'Kehamilan dan Menyusui'.
  Pasien dianjurkan untuk mulai pada hari ke-21 sampai ke-28 setelah melahirkan atau setelah keguguran pada trimester kedua.
  Jika mulai setelah itu, pasien dianjurkan untuk menggunakan kontrasepsi metode penghalang tambahan selama 7 hari pertama minum tablet. Akan tetapi jika sudah melakukan hubungan seks, kehamilan harus dipastikan tidak terjadi sebelum mulai minum Diane-35 atau pasien harus menunggu sampai masa menstruasinya yang pertama.

Mengatasi lupa minum tablet

Jika pasien terlambat minum tablet **kurang dari 12 jam**, daya perlindungan kontrasepsinya tidak berkurang. Tablet harus segera diminum setelah ia ingat, dan tablet berikutnya kembali diminum pada waktu biasa.

Jika pasien terlambat minum tablet **lebih dari 12 jam**, daya perlindungan kontrasepsinya mungkin berkurang.

Penanganan lupa minum tablet dapat mengikuti dua aturan dasar berikut ini:

1. Pemakaian tablet harus terus dilanjutkan lebih dari 7 hari.
2. 7 hari pemakaian tablet yang terus menerus diperlukan untuk mendapatkan penekanan yang memadai pada poros hipotalamus-pituitari-indung telur.

Dengan demikian, saran berikut dapat diberikan dalam praktek sehari-hari:

- ▶ *Minggu-ke 1*
  Pasien harus segera minum tablet yang terlupa, meskipun berarti minum dua tablet secara bersamaan. Tablet berikutnya diminum pada waktu biasa. Sebagai tambahan, supaya dipunakan kontrasepsi metode penghalang seperti kondom selama 7 hari berikutnya. Jika terjadi hubungan seks dalam masa 7 hari sebelumnya, kemungkinan terjadinya kehamilan harus dipertimbangkan. Makin banyak tahap yang terlupa dan makin dekat terlupanya ke masa minum tablet plasebo, makin tinggi risiko terjadinya kehamilan.
- ▶ *Minggu ke-2*
  Pasien harus segera minum tablet yang terlupa, meskipun berarti minum dua tablet secara bersamaan. Tablet berikutnya diminum pada waktu biasa. Jika pasien tersebut sudah minum tabletnya secara benar dalam masa 7 hari sebelum tablet yang terlupa, tidak perlu menggunakan kontrasepsi tambahan. Tetapi, kalau bukan demikian yang terjadi, atau jika dia lupa minum lebih dari 1 tablet, pasien dianjurkan untuk menggunakan kontrasepsi tambahan selama 7 hari.
- ▶ *Minggu ke-3*
  Risiko berkurangnya efektifitas sangat nyata karena makin mendekatnya masa minum tablet plasebo. Walaupun demikian, dengan mengatur jadwal minum tablet, berkurangnya perlindungan kontrasepsi dapat dicegah. Dengan mengikuti salah satu dari dua pilihan berikut, tidak perlu menggunakan kontrasepsi tambahan, asalkan dalam masa 7 hari sebelum tablet yang pertama terlupa, semua tablet sudah diminum dengan benar. Jika tidak demikian, pasien dianjurkan agar mengikuti pilihan pertama dan dua pilihan berikut ini dan untuk menggunakan pencegahan tambahan untuk masa 7 hari berikutnya.
  1. Pasien harus minum tablet yang terlupa segera setelah dia mengingatnya, walaupun ini berarti harus minum dua tablet secara bersamaan. Tablet selanjutnya diminum seperti biasa. Kemasan berikutnya harus segera mulai diminum setelah kemasan sebelumnya selesai, supaya tidak ada lagi tablet yang terlupa. Pasien tidak akan mengalami perdarahan lucut sampai tablet aktif dari kemasan kedua habis, tetapi mungkin mengalami perdarahan bercak atau perdarahan antar siklus dalam masa minum tablet.
  2. Pasien dapat juga dianjurkan untuk menghentikan minum tablet dari kemasan yang sekarang. Kemudian melakukan masa bebas tablet sampai 7 hari, termasuk hari dimana dia lupa minum tablet, dan kemudian dilanjutkan dengan kemasan berikutnya.

Jika pasien lupa minum tablet dan setelah itu tidak mengalami perdarahan lucut pada masa minum tablet plasebo, kemungkinan terjadinya kehamilan harus dipertimbangkan.

Saran untuk kasus gangguan lambung

Dalam kasus gangguan lambung parah, absorpsi mungkin tidak sempurna dan sebaiknya digunakan alat kontrasepsi tambahan.

Jika terjadi muntah–muntah dalam waktu 3-4 jam setelah minum tablet, anjuran mengenai lupa minum tablet pada bagian 'mengatasi lupa minum tablet' dapat diberlakukan. Jika pasien tidak mau merubah jadwal minum tabletnya yang normal, dia harus minum tablet tambahan yang diperlukan dari kemasan lain.

Lama penggunaan

Lama penggunaan tergantung pada beratnya gejala androgenisasi dan respons pada pengobatan. Pada umumnya, obat harus diberikan selama beberapa bulan. Waktu untuk meringankan gejala-gejala tersebut diutilisasikan paling tidak tiga bulan. Jerawat dan seborea biasanya bereaksi lebih cepat dibandingkan hirsutisme. Kebutuhan untuk melanjutkan pengobatan harus dievaluasi secara berkala oleh dokter yang merawat.

Jika tertjadi kekambuhan gejala-gejala beberapa minggu atau bulan setelah tablet dihentikan, pemberian Diane-35 dapat dilanjutkan. Peningkatan risiko VTE pada saat mulai menggunakan Diane-35 kembali (setelah 4 minggu atau interval yang lebih panjang) harus dipertimbangkan (lihat bagian "Peringatan dan perhatian khusus penggunaan).

Informasi tambahan pada populasi khusus

Pasien Geriatri

Tidak diperuntukkan. Diane-35 tidak diindikasikan setelah menopause

Pasien dengan gangguan hati

Diane-35 dikontraindikasikan pada wanita dengan penyakit hati parah. Lihat pada bagian "Kontraindikasi"

Pasien dengan gangguan ginjal

Tidak dilakukan penelitian secara spesifik pada pasien dengan gangguan ginjal. Data yang tersedia tidak memperlihatkan perubahan pengobatan pada populasi ini.

Kontraindikasi

Kombinasi estrogen/progestogen tidak boleh digunakan jika ada kondisi-kondisi di bawah ini. Jika kondisi tersebut tertjadi pertama kali sejak menggunakan KOK, produk tersebut harus segera dihentikan.

- ▶ Terdapat atau dengan riwayat trombosis/tromboemboli vena atau arteri (misal trombosis vena dalam, emboli paru, infark miokard) atau serangan pada pembuluh darah otak.
- ▶ Terdapat atau dengan riwayat prodromi trombosis (misal serangan iskemik sementara, angina pektoris).
- ▶ Adanya risiko tinggi trombosis vena atau arteri (lihat 'Peringatan dan perhatian khusus penggunaan').
- ▶ Riwayat migrain dengan gejala-gejala neurologis fokal.
- ▶ *Sickle-cell* anemia
- ▶ Diabetes mellitus dengan kelainan vaskular.
- ▶ Penggunaan produk obat-obat lain secara aktif-langsung yang mengandung ombitasir, paritaprevir or dasabouvir ini dan kombinasinya (lihat "Interaksi dengan obat lain dan bentuk interaksi lain")
- ▶ Penyakit hati yang parah selama fungsi hati belum kembali normal.
- ▶ Ada atau dengan riwayat tumor hati (jinak maupun ganas).

- ▶ Diketahui atau diduga adanya keganasan yang dipengaruhi oleh hormon seks (misal pada organ kelamin atau payudara).
- ▶ Penggunaan bersama dengan kontrasepsi hormonal lain (lihat bagian Indikasi)
- ▶ Pendarahan vagina yang tidak diketahui.
- ▶ Diketahui atau diduga adanya kehamilan.
- ▶ Menyusui
- ▶ Hipersensitif terhadap zat aktif atau zat tambahan.

Diane-35 tidak diperuntukkan untuk pria.

Peringatan dan perhatian khusus selama penggunaan

Diane-35 terdiri dari progestogen siproteron asetat dan estrogen etinilestradiol dan diberikan selama 21 hari dari siklus bulanan. Diane-35 memiliki komposisi yang sama dengan kontrasepsi oral kombinasi (KOK).

Pengalaman klinis dan epidemiologis dengan kombinasi estrogen/progestogen seperti Diane-35 terutama didasarkan pada kontrasepsi oral kombinasi (KOK). Karena itu peringatan berlisir terkait penggunaan KOK juga berlaku untuk Diane-35.

Peringatan

Jika ada kondisi/faktor risiko berikut, rasio manfaat-risiko pemberian Diane-35 harus dipertimbangkan secara individu dan dibicarakan dengan pasien tersebut sebelum dia memutuskan untuk mulai menggunakannya. Dalam hal bertambahnya, memburuknya atau kemunculan pertama dari kondisi atau faktor risiko berikut, pasien harus segera menghubungi dokternya.

Dokter selanjutnya akan memutuskan apakah Diane-35 harus dihentikan.

Gangguan peredaran darah

Studi epidemiologis menunjukkan kaitan antara penggunaan KOK dengan peningkatan risiko penyakit trombosis arteri dan vena, serta penyakit-penyakit tromboemboli seperti infark miokard, stroke, trombosis vena dalam, embolisme paru, dan serangan pembuluh darah otak. Kasus-kasus tersebut jarang tejadi.

Risiko VTE paling tinggi terjadi pada tahun pertama penggunaan KOK. Peningkatan risiko tergadi pada saat awal atau mulai menggunakan KOK kembali (setelah 4 minggu atau interval yang lebih panjang) dengan menggunakan KOK yang sama atau berbeda. Data dari Studi *Cohort* besar prospektif pada 3 kelompok memperlihatkan bahwa peningkatan risiko tergadi selama 3 bulan pertama.

Secara keseluruhan risiko tromboemboli vena (VTE) pada pengguna KOK yang mengandung estrogen dosis rendah (<50 µg etinilestradiol) adalah dua sampai tiga kali lebih besar dibandingkan bukan pengguna KOK yang tidak hamil dan masih sangat rendah risikonya dalam kaitannya dengan kehamilan dan melahirkan.

VTE dapat mengancam jiwa atau mungkin berakibat fatal (pada 1-2% kasus yang terjadi).

Tromboemboli vena (VTE), bermanifestasi sebagai trombosis vena dalam dan/atau emboli paru, yang dapat terjadi selama penggunaan semua KOK.

Pada pengguna KOK, jarang sekali trombosis dilaporkan terjadi di pembuluh-pembuluh darah lain, misal hati, *mesenteric*, ginjal, otak atau vena dan arteri retina. Belum ada konsensus apakah kasus-kasus ini berhubungan dengan penggunaan KOK.

Gejala-gejala trombosis vena dalam (DVT) dapat berupa: pembengkakan tungkai unilateral atau sepanjang vena pada tungkai, nyeri atau bengkak pada kaki ketika berdiri atau berjalan, rasa panas pada kaki yang terserang, kulit pada kaki berwarna merah atau pucat.

Gejala-gejala emboli paru (PE) dapat berupa: nafas pendek atau sesak nafas mendadak, batuk mendadak yang disertai darah, nyeri didada disertai peningkatan nafas yang dalam, cemas, sakit kepala berat atau pusing, denyut jantung kencang atau tidak teratur. Beberapa dari gejala tersebut (misal nafas pendek, batuk) tidak spesifik dan dapat diartikan sebagai gejala yang umum dan tidak parah (seperti infeksi saluran pernafasan).

Serangan tromboemboli arteri berupa serangan pembuluh darah otak, oklusi vaskular atau infark miokard.

Gejala serangan pembuluh darah otak dapat berupa: kesemutan atau lemah pada wajah, lengan atau kaki mendadak, terutama pada satu sisi bagian tubuh, mendadak bingung, susah berbicara atau mengerti, gangguan penglihatan sebagian atau seluruhnya, susah berjalan, pusing, berkurang kesiembangan atau koordinasi, mendadak sakit kepala yang tiba-tiba, parah, atau berkepanjangan tanpa diketahui penyebabnya, hilangnya kesadaran atau pingsan. Gejala lain oklusi vaskular berupa: nyeri mendadak, bengkak ,dan memar pada tangan dan kaki, sakit perut akut.

Gejala-gejala infark miokard dapat berupa: nyeri, kegelisahan, tekanan, atau rasa sesak pada dada, lengan atau bagian bawah tulang dada; sakit pada bagian punggung, rahang, tenggorokan, lengan, perut; kembung; gangguan pencernaan atau rasa sesak; berkeringan, mual, muntah atau pusing, rasa lemah cemas, sesak nafas, denyut jantung tidak teratur dan kencang.

Tromboemboli arteri dapat mengancam jiwa atau mungkin berakibat fatal.

Potensi peningkatan risiko trombosis yang sinergis harus dipertimbangkan pada wanita yang mempunyai faktor risiko atau memperlihatkan adanya keparahan yang lebih besar pada faktor risiko individu.

Peningkatan risiko ini mungkin lebih besar daripada risiko kumulatif yang sederhana pada faktor-faktor tersebut. Tidak diperbolehkan peresepan Diane-35 pada kasus penjalasan mamfaat risiko yang negatif (lihat "Kontraindikasi").

Risiko trombotik/tromboemboli vena atau arteri atau serangan pada pembuluh darah otak dapat meningkat dengan:

- ▶ usia;
- ▶ obesitas (Indeks massa tubuh diatas 30 kg/m²);
- ▶ riwayat keluarga yang positif (misal tromboemboli vena atau arteri pada saudara atau orangtua kandung pada usia relatif muda). Jika diketahui atau diduga ada kecenderungan faktor keturunan, pasien harus dirujuk ke dokter spesialis sebelum memutuskan untuk menggunakan KOK;
- ▶ lumpuh berkepanjangan, operasi besar, operasi pada kaki, atau trauma besar. Pada situasi tersebut penggunaan KOK sebaiknya dihentikan (pada kasus pembedahan yang direncanakan, paling sedikit dihentikan empat minggu sebelumnya) dan tidak dimulai penggunaan KOK lagi selama dua minggu setelah rembolisasi sempurna;
- ▶ merokok (perokok berat dan pertambahan usia lebih meningkatkan risiko, terutama pada wanita di atas usia 35 tahun);
- ▶ dislipoproteinemia
- ▶ hipertensi;
- ▶ migren
- ▶ kelainan katup jantung;
- ▶ fibrilasi atrium;

Belum ada konsensus tentang peranan dari varises vena dan tromboflebitis superficial pada tromboemboli vena.

Peningkatan risiko tromboemboolisme pada puerperium harus dipertimbangkan (untuk informasi pada kehamilan dan menyusui lihat bagian 'Kehamilan dan Menyusui').

Kelompok penggunaa Diane-35 kemungkinan juga mencakup pasien yang mungkin memiliki hubungan erat dengan peningkatan risiko kardiovaskular seperti yang terkait dengan diabetes polikistik ovarium.

Kondisi medis lain yang terkait dengan gangguan peredaran darah termasuk diabetes mellitus, lupus eritematosus sistemik, sindrom uremik hemolitik, penyakit radang usus kronik (penyakit Crohn atau kolitis ulserative) dan penyakit *sicle cell*.

Peningkatan frekuensi atau keparahan migren selama penggunaan Diane-35 (gejala awal dari kasus kelainan pembuluh darah otak) dapat menjadi alasan untuk segera menghentikan pemakaian Diane 35.

Faktor biokimia yang bisa menunjukkan kecenderungan bawaan atau kecenderungan untuk mengalami trombosis vena atau arteri termasuk resistensi protein aktif C (APC), hiperhomosisteinemia, defisiensi antitrombin-III, defisiensi protein C, defisiensi protein S, antibodi antifosfolipid (antibodi antikardiolipin, antikoagulan lupus).

Dalam mempertimbangkan risiko/manfaat, dokter harus mempertimbangkan bahwa pengobatan tertentu dapat mengurangi risiko timbulnya trombosis dan risiko yang disebabkan oleh kehamilan lebih tinggi daripada yang disebabkan oleh pemakaian KOK dosis rendah (<0,05 mg etinilestradiol).

Tumor

Faktor risiko terpenting untuk kanker mulut rahim adalah infeksi HPV yang menetap. Beberapa studi epidemiologi menunjukkan bahwa penggunaan KOK jangka lama berperan dalam peningkatan risiko ini, tetapi masih terdapat kontroversi tentang pengaruh temuan ini pada efek-efek terkait, seperti skrining mulut rahim dan perilaku seksual, termasuk penggunaan kontrasepsi penghalang.

Suatu meta analisa dari 54 studi epidemiologi melaporkan bahwa terdapat sedikit peningkatan risiko relatif (RR = 1,24) kanker payudara pada pengguna KOK. Peningkatan risiko ini berkurang secara bertahap setelah 10 tahun berhenti menggunakan KOK. Karena kanker payudara jarang terjadi pada wanita berusia di bawah 40 tahun, jumlah yang terdiagnosa kanker payudara pada pengguna atau pernah menggunakan KOK lebih kecil dibandingkan risiko keseluruhan kanker payudara. Studi-studi tersebut tidak dapat memberi bukti tentang penyebabnya. Pola peningkatan risiko ini mungkin karena diagnosis dini kanker payudara pada pengguna KOK, efek biologis dari KOK, atau keduanya. Secara klinis, diagnosis kanker payudara pada pengguna cenderung lebih ringan dibanding kanker yang didiagnosa pada yang belum pernah menggunakan.

Kasus tumor hati yang jinak jarang, dan tumor hati yang ganas lebih jarang lagi dilaporkan pada pengguna KOK. Pada kasus tertentu, tumor-tumor tersebut menyebabkan perdarahan intra-abdominal yang membahayakan jiwa. Tumor hati harus dipertimbangkan pada diagnosa banding bila terdapat nyeri hebat pada perut bagian atas, pembengkakan hati, atau tanda-tanda perdarahan intra-abdominal pada wanita pengguna KOK.

Keganasan dapat mengancam jiwa atau mungkin berakibat fatal.

Kondisi lainnya

Risiko pankreatitis dapat meningkat pada pasien dengan hipertrigliseridemia, atau dengan riwayat hipertrigliseridemia, yang menggunakan KOK.

Peningkatan tekanan darah walaupun sedikit pernah dilaporkan terjadi pada banyak pasien yang menggunakan KOK, peningkatan yang relevan secara klinis jarang terjadi. Walaupun demikian, jika terjadi kenaikan tekanan darah yang bermakna secara klinis dan terus menerus selama penggunaan KOK, maka sebaiknya dokter mempertimbangkan penggunaan KOK dan mengobati hipertensinya. Jika dianggap perlu, KOK dapat diberikan lagi setelah tekanan darah normal kembali dengan pengobatan antihipertensi.

Kondisi-kondisi berikut pernah dilaporkan terjadi atau memburuk baik pada kehamilan maupun penggunaan KOK, tetapi bukti keterkaitannya dengan penggunaan KOK tidak dapat disimpulkan: ikterus dan/atau pruritus terkait kolestasis; pembentukan batu empedu; porfiria; sistemik lupus eritematosus; sindroma hemolitik uremik; *Sydenham's chorea*; herpes gestationis; gangguan pendengaran karena otosklerosis.

Pada wanita dengan angioedema herediter, estrogen eksogen dapat memicu atau menimbulkan kembali gejala-gejala angioedema.

Penggunaan KOK harus dihentikan pada gangguan fungsi hati akut atau kronik sampai fungsi hati kembali normal. KOK juga harus dihentikan jika terjadi kekambuhan ikterus kolestatik selama kehamilan atau penggunaan hormon seks sebelumnya.

Meski KOK dapat mempengaruhi resistensi insulin perifer dan toleransi glukosa, tidak ada bukti yang menyatakan perlunya mengubah regimen terapetik penggunaan KOK dosis rendah (mengandungi <0,05 mg etinilestradiol) pada pasien diabetes. Tetapi wanita penderita diabetes harus dimonitor secara ketat ketika menggunakan KOK.

Penyakit Crohn dan kolitis ulserratif telah dikaitkan dengan penggunaan KOK.

Kadang kala kloasma bisa terjadi, terutama pada wanita dengan riwayat kloasma gravidarum. Pasien dengan kecenderungan kloasma harus menghindari paparan sinar matahari atau sinar ultraviolet ketika menggunakan KOK.

Pada wanita pengidap hirsutisme, jika gejala semakin berkembang atau meningkat secara substansial, penyebabnya (tumor pembentuk androgen, kelainan enzim adrenal) harus diklarifikasi dalam diagnosis differensial.

Setiap tablet salut yang mengandung 31 mg laktosa per tablet. Pasien dengan riwayat intoleransi galaktosa, defisiensi *Lapp lactase* atau malabsorpsi glukosa-galaktosa yang diet bebas laktosa harus mempertimbangkan jumlah laktosa tersebut.

Pemeriksaan/konsultasi medis

Riwayat medis dan pemeriksaan fisik menyeluruh harus dilakukan sebelum memulai atau pemakaian kembali Diane-35, dipandu oleh kontraindikasi (bagian 'Kontraindikasi') dan peringatan (bagian 'Peringatan'), harus dilaung serta berkala. Evaluasi medis secara berkala juga penting karena kontraindikasi (mis. serangan iskemik sementara, dsb.) atau faktor risiko (mis. riwayat trombosis vena atau arteri dalam keluarga) dapat terjadi untuk pertama kalinya ketika menggunakan Diane-35. Frekuensi dan sifat pemeriksaan harus didasarkan pada petunjuk pemakaian yang berlaku dan disesuaikan dengan untuk setiap individu wanita, tetapi biasanya mencakup rujukan khusus mengenai pemeriksaan tekanan darah, payudara, organ perut dan panggul termasuk sitologi serviks.

Wanita harus diberitahu bahwa obat seperti Diane-35 tidak memberikan perlindungan terhadap infeksi HIV (AIDS) dan penyakit-penyakit seksual menular lainnya.

Penurunan efikasi

Efek kontrasepsi Diane-35 dapat berkurang, mis. pasien lupa minum tablet (bagian 'Mengatasi lupa minum tablet'), gangguan lambung (bagian 'Saran pada gangguan lambung') selama minum tablet atau pengobatan secara bersamaan (bagian 'Interaksi dengan obat lain dan bentuk interaksi lain').

Penurunan kontrol siklus haid

Dengan kombinasi estrogen/progestogen, hadi tidak teratur (perdarahan bercak atau perdarahan antar siklus) dapat terjadi, terutama dalam bulan pertama penggunaan. Karena itu, evaluasi haid tidak teratur harya bermakna setelah adaptasi sekitar tiga siklus.

Jika haid tidak teratur bertahan atau terjadi setelah siklus haid yang teratur sebelumnya, perlu dipertimbangkan penyebab non-hormonal dan dilakukan tindakan diagnostik yang memadai untuk menghindari adanya keganasan atau kehamilan. Tindakan ini dapat berupa kuretase.

Pada sebagian wanita, haid mungkin tidak terjadi selama fase tablet inert. Jika KOK diminum sesuai petunjuk yang diberangkan dalam bagian 'Dosis dan cara pemberian', wanita tersebut kemungkinan tidak hamil. Tetapi jika KOK tidak diminum dengan benar sebelum perdarahan lucut berhenti sebanyak satu atau dua kali, kemungkinan hamil harus dipastikan tidak terjadi sebelum penggunaan KOK dilanjutkan.

Alasan untuk segera menghentikan pemakaian Diane-35:

- ▶ Kejadian pertama kali, atau memburuknya migrain, atau sakit kepala yang parah yang tidak seperti biasanya.
  - ▶ Gangguan penglihatan, pendengaran, atau gangguan persepsi lainnya yang tibatiba.
  - ▶ Gejala awal tromboflebitis atau tromboemboolisme (misal nyeri yang tidak biasa atau pembengkakan pada kaki, nyeri dada saat bermafas atau batuk tanpa sebab yang jelas). Rasa sakit atau sesak di dada.
  - ▶ Enam minggu sebelum operasi besar (misal operasi abdomen, operasi ortopedi), operasi pada kaki, terapi medis untuk varises vena atau lumpuh berkepanjangan, seperti pasca kecelakaan atau operasi. Jangan mulai menggunakan sampai 2 minggu setelah benar benar pulih. Dalam hal operasi darurat, trombosis profilaksis biasanya diindikasikan seperti subkutan heparin.
  - ▶ Mulai timbul gejala ikterus, hepatitis, gatal di seluruh tubuh.
  - ▶ Peningkatan serangan epilepsi.
  - ▶ Peningkatan tekanan darah yang signifikan.
  - ▶ Timbulnya depresi berat.
  - ▶ Nyeri perut bagian atas yang hebat atau pembesaran hati.
  - ▶ Memburuknya kondisi yang diketahui dapat menjadi parah selama pemakaian kontrasepsi oral atau kehamilan.
  - ▶ Kehamilan menjadi alasan untuk segera menghentikan penggunaan obat karena berbagai penelitian pada kaki, nyeri dada saat bermafas oral yang dimunum pada awal kehamilan dapat sedikit meningkatkan risiko cacat janin. Penelitian lainnya tidak mendukung penemuan ini. Namun demikian kemungkinan ini tidak dapat diabaikan, tetapi yang pasti bahwa jika risiko ini ada, risikonya sangat kecil.

Perhatian

Kondisi-kondisi berikut perlu mendapatkan perhatian medis khusus jika diberikan dengan kontrasepsi oral. Memburuknya atau kemunculan pertama dari kondisi tersebut mendasakan bahwa Diane-35 harus dihentikan.

- ▶ Diabetes mellitus, atau kecenderungan adanya diabetes mellitus (misalnya glikosuria yang tidak dapat diterangkan), hipertensi, varises vena, riwayat flebitis, otosklerosis, multipel sklerosis, epilepsi, porfiria, tetanus, gangguan fungsi hati, Sydenham's chorea, disfungsi ginjal, riwayat gangguan pembekuan darah dalam keluarga, kegemukan, riwayat kanker payud