Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

Diane-35, 0.035 mg/2 mg coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances: ethinylestradiol / cyproterone acetate

Each coated tablet contains 0.035 mg of ethinylestradiol and 2 mg of cyproterone acetate.

Excipients:
Lactose monohydrate 31 mg, sucrose 19 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet, beige

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe acne due to androgen sensitivity (with or without seborrhoea) and/or hirsutism in women of childbearing age.

Diane-35 should be used only after the failure of topical therapy or systemic antibiotic treatments for acne therapy.

As Diane-35 is also a hormonal contraceptive, it must not be used in combination with other hormonal contraceptives (see section 4.3).

4.2 Posology and method of administration

Diane-35 inhibits ovulation and thereby has a contraceptive effect. Patients who are using Diane-35 should, therefore, not use an additional hormonal contraceptive, since this leads to an overdose of hormones and is not necessary for effective contraceptive protection.
For the same reason, women who desire to become pregnant should not use Diane-35. Diane-35 must be taken regularly in order to develop an adequate therapeutic efficacy and effective contraceptive protection.

Method of administration
Oral use

Posology
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 withdrawal bleeding usually occurs, which often starts on the 2nd-3rd day after taking the last tablet and can continue until the next pack is started.

Contraceptive protection starts on the first day the tablets are taken and also continues during the 7 tablet-free days. The simultaneous use of hormonal contraceptives must therefore stop.

Medical examination/consultation
Before using, it is advisable to perform a thorough general medical examination (including body weight, blood pressure, heart, legs and skin, urine test for diabetes, and liver diagnostic tests when necessary) as well as gynaecological examinations (including the breasts and a cytological smear taken from the vaginal portion of the cervix and the cervix) and to compile a thorough family medical history in order to be able to detect diseases requiring treatment and risks. Pregnancy must be ruled out. It is advisable to have checkups every six months during use.
Coagulation system disorders should be ruled out if thromboembolic events (e.g. deep venous thrombosis, stroke, heart attack) have occurred in blood relatives at an early age.

It should also be pointed out that taking oral contraceptives does not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Starting treatment

No previous hormonal contraception (during the past month)
Tablet taking of one tablet daily has to start on day 1 of the woman's natural cycle (the first day of her menstrual bleeding). If the course is started between days 2 and 5, an additional contraceptive precaution (barrier contraceptive) is recommended during the first 7 days of tablet taking.

Only amenorrhoeic women start treatment immediately as prescribed by their physician; in the case of which, the first day of tablet taking is equivalent to the first day of the menstrual cycle and counting is continued according to the following recommendations.

Having previously taken combined oral contraceptives or having used a vaginal ring or a transdermal patch
Diane-35 should preferably be started on the day after having taken the last hormone-containing tablet of the previous combination product (or after the removal of the ring or of the patch), but at the latest on the day after the usual tablet-free interval, or on the day after having taken the last placebo from the previous combination product. If a ring or patch has previously been used, Diane-35 should preferably be started on the day upon removal of the last ring/last patch of a cycle pack, but at the latest on the day when re-administration of the previous contraceptive would be necessary.

Changing from a progestagen-only product (minipill, injection, implant) or from an intrauterine system (IUS)
If the minipill has been taken previously, Diane-35 can be started on any day (the change from an implant or intrauterine system must take place on the day of removal, and at the time the next injection would be due, when changing from an injectable contraceptive). However, in all cases, additional contraceptive precautions are required during the first 7 days of tablet use.

After a first-trimester abortion
The tablets can be started immediately. In this case, no additional contraceptive precautions are required.

After delivery or a second-trimester abortion
The tablets should be started on days 21 to 28 after delivery or after an abortion in the second trimester. If they are started later, an additional barrier contraceptive must be used during the first 7 days of tablet taking. If, however, sexual intercourse has already taken place, pregnancy must be ruled out or the first menstrual period must have occurred before starting use.

Duration of administration
The time to symptomatic relief is at least three months. The treating physician should regularly check whether there is still a need for treatment.

The length of use depends on the severity of the symptoms of androgenisation and the response to treatment. Acne and seborrhoea usually respond sooner than hirsutism. It is recommended to take Diane-35 for at least another 3 to 4 cycles after the signs have subsided.

If there has been a lack of response or only insufficient response in treating
- severe acne or seborrhoea for at least six months or
- hirsutism for at least 12 months

achieved, combined use of Diane-35 and Androcur 10 mg tablets or Androcur 50 mg tablets has to be considered or rather the treatment approach has to be reconsidered.

As soon as the androgenisation signs have subsided but contraception is still desired, maybe a switch should be made to a low-dose oral contraceptive. Should there be a recurrence of androgenic symptoms, treatment with Diane-35 can be resumed. When resuming treatment with Diane-35 (after a tablet-free interval of at least 4 weeks), the increased risk of venous thromboembolism should be considered (see section 4.4).

How to proceed when a tablet has been missed
If a user of Diane-35 forgot to take a tablet at the usual time, it has to be taken within 12 hours. All subsequent tablets should then be taken again at the usual time. Contraceptive protection is not impaired.

If it has been more than 12 hours, contraception is no longer reliable. When tablets have been forgotten, there are basically two things to bear in mind:

1. Tablet taking must never be interrupted for longer than 7 days.
2. In order to build up adequate contraceptive protection, i.e. to achieve suppression of the hypothalamic-pituitary-ovarian system, it is necessary to take the tablets for 7 days.

Accordingly, the following recommendations can be made for routine practice.

Week 1
The missed tablet should be taken as soon as possible, even if this means taking two tablets at the same time. The remaining tablets are then taken at the usual time. During the next 7 days, however, an additional barrier contraceptive, such as a condom, should be used. If sexual intercourse has taken place in the past 7 days, the possibility of pregnancy should be taken into consideration. The risk of pregnancy is all the higher, the more tablets have been forgotten and the closer this is to the regular tablet-free interval.

Week 2
Die The missed tablet should be taken as soon as possible, even if this means taking two tablets at the same time. The remaining tablets are then taken at the usual time. Provided that the tablets have been taken correctly on the 7 days before the first missed tablet, there is no need to use additional protective measures. If this was not the case or if more than 1 tablet was forgotten, the use of additional protective measures for 7 days should be recommended.

Week 3
On account of the approaching 7 tablet-free days, complete contraceptive protection can no longer be guaranteed. On the other hand, reduction of the contraceptive effect can be prevented by adjusting the tablet-taking schedule. By adhering to either of the two following procedures, there is no need for additional contraceptive measures, provided that the tablets were taken correctly on the 7 days preceding the first missed tablet. If this is not the case, the woman should proceed as described in item 1 and also use additional protective measures during the next 7 days.

1. The user should make up for the last missed tablet as soon as possible, even if this means taking two tablets at the same time. The remaining tablets are then taken at the usual time. The next blister pack is started directly after completion of the current blister pack, i.e. there should be no

tablet-free interval between the two packs. It is unlikely that the user will have withdrawal bleeding before completing the second pack, however spotting or breakthrough bleeding can occur during use.

2. It can also be recommended to stop taking tablets from the current blister pack, followed by a tablet-free interval of up to 7 days, including the days on which tablets were omitted. The next pack should then be started.

In the event of missed tablets and missed withdrawal bleeding during the next regular tablet-free interval, the possibility of pregnancy should be considered.

Absence of withdrawal bleeding
in the absence of withdrawal bleeding, use should be discontinued until pregnancy has been excluded with certainty.

How to proceed in the case of intermenstrual bleeding
It is imperative to continue taking Diane-35 in the event of intermenstrual bleeding. Spotting usually ceases spontaneously or can be resolved within 4 to 5 days - as can intermenstrual bleeding of menstrual intensity (breakthrough bleeding) - by the additional administration of 25 - 50 µg of ethinyl estradiol (but not extending beyond the last tablet in a pack of Diane-35).
If breakthrough bleeding does not cease or if it recurs, a thorough examination to exclude an organic cause is indicated, including curettage.
This also applies to spotting, which occurs at irregular intervals in several consecutive cycles or which occurs for the first time after long use of Diane-35. In these cases, the bleeding is usually caused by organic changes and not by the product.

How to proceed in the case of vomiting or severe diarrhoea
Vomiting or severe diarrhoea may lead to incomplete absorption of the active ingredients. Additional non-hormonal methods of contraception (except the rhythm or temperature methods) should be used. If vomiting or severe diarrhoea occur within 3 to 4 hours after tablet taking, The procedure quoted with regard to missed tablets in Section 4.2 "Dosage and method of administration" should be followed. If the user concerned does not want to depart from her normal tablet-taking rhythm, she must take the replacement tablet(s) from another blister pack.

Liver
After recovering from viral hepatitis (when the liver parameters have returned to normal), approximately six months should elapse before using a product, such as Diane-35.

Additional information on certain patient groups

Children and adolescents
Diane-35 may only be used after the menarche.

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

Patients with hepatic dysfunction
Diane-35 is contraindicated in women with severe hepatic disease, as long as liver function values have not returned to normal. See also section 4.3.

Patients with renal dysfunction
Diane-35 has not been specifically studied in patients with impaired renal function. The available data do not indicate the need for any treatment adjustment in this patient group.

4.3 Contraindications

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

- Concomitant use of another hormonal contraceptive (see section 4.1),
- Existing or previous venous thrombosis (e.g. deep vein thrombosis, pulmonary embolism),
- Personal or family medical history of known, idiopathic venous thromboembolism (VTE) (where the family medical history relates to VTE in a sibling or parent at a relatively early age),
- Existing or previous arterial thrombosis (e.g. myocardial infarction) or previous disorders (e.g. angina pectoris and transient ischemic attack),
- Existing or previous cerebrovascular accident,
- Presence of severe or multiple risk factors for venous or arterial thrombosis (see section 4.4), e.g.:
  - diabetes mellitus with vascular symptoms
  - severe hypertension
  - severe dyslipoproteinaemia
- Inherited or acquired predisposition for venous or arterial thrombosis, e.g. resistance to activated protein C (APC resistance), antithrombin III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant),
- Sickle cell anaemia,
- Severe hepatic disorders (also disorders of the excretory system such as Dubin-Johnson and Rotor syndrome) as long as the liver function values have not returned to normal,
- Presence or a history of liver tumours (benign or malignant),
- Undiagnosed vaginal bleeding,
- History of migraine with focal neurological symptoms,
- Smokers (see Section 4.4),
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts),
- Meningioma or history of meningioma,
- History of idiopathic jaundice of pregnancy, severe pruritus of pregnancy or herpes gestationis, otosclerosis worsening in previous pregnancies,
- Presence of a desire for pregnancy, pregnancy, breast-feeding,
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Diane-35 is not for use in men.

Diane-35 is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir plus dasabuvir or medicinal products containing glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

4.4 Special Warnings and Special Precautions for Use

Diane-35 consists of the progestogen cyproterone acetate and the oestrogen ethinylestradiol and is administered for 21 days of a monthly cycle. It has a composition similar to a combined oral contraceptive (COC).

Duration of administration
The time to symptomatic relief is at least three months. The treating physician should regularly check whether there is still a need for treatment (see section 4.2).

If any of the disorders/risk factors mentioned below are present, the benefit of using Diane-35 should be weighed against the possible risks for the woman and discussed with her before she decides to use Diane-35. In the event of aggravation/exacerbation or first appearance of any of these disorders or risk

factors, the woman should contact her physician. The physician should then decide whether the use of Diane-35 should be terminated.

Circulatory diseases

- The use of Diane-35 carries an increased risk of venous thromboembolism (VTE) compared with non-use. The additional VTE risk is greatest during the first year of initial Diane-35 use by a woman or upon resumed use or a switch after a pill-free interval of at least one month. A venous thromboembolism can be fatal in 1 - 2% of cases.

- Epidemiological studies have shown that the incidence of VTE in users of Diane-35 is 1.5 to 2 times higher than in users of combined oral contraceptives (COCs) containing levonorgestrel and may be similar to the risk for COCs containing desogestrel/gestodene/drospirenone.

- The Diane-35 user group is likely to include patients who have a congenital increased cardiovascular risk, e.g. due to polycystic ovary syndrome.

- Furthermore, epidemiological studies have associated the use of hormonal contraceptives with an increased risk for arterial (myocardial infarction, transient ischemic attack) thromboembolism.

- In very rare cases, thrombosis has been reported to occur in other blood vessels among users of hormonal contraceptives, e.g. arteries and veins of the liver, mesentery, kidney, brain or retina.

- The following may occur as symptoms of venous or arterial thrombosis or a cerebrovascular accident: unusual unilateral leg pain and/or swelling; sudden severe chest pain, regardless of whether it radiates to the left arm; sudden dyspnoea; sudden onset of cough; any unusual, severe, persistent headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without a focal seizure; weakness or very significant numbness suddenly affecting one side or one part of the body; motor disorders; “acute” abdomen

- The risk of venous thromboembolic events rises with:
  - increasing age;
  - smoking (the risk increases further with increasing tobacco consumption and age, especially in women over 35 years of age. Women over 35 years of age should be strongly advised not to smoke if they wish to use Diane-35;
  - a positive family history (i.e. venous thromboembolism in a sibling or parent at a relatively young age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before making a decision regarding the use of a hormonal contraceptive;
  - prolonged bed confinement, major surgery, leg surgery or severe trauma. In these situations, it is recommended that use be terminated (in case of elective surgery, at least four weeks in advance) and not resumed until two weeks after full mobility has been regained. If the use of Diane-35 has not been terminated in advance, therapy with an antithrombotic agent should be considered;
  - obesity (body mass index over 30 kg/m^2).

- The risk of arterial thromboembolic complications or cerebrovascular accident rises with:
  - increasing age;
  - smoking (the risk rises further with increasing tobacco consumption and age, especially in women over 35 years of age. Women over 35 years of age should be strongly advised not to smoke if they wish to use Diane-35);
  - dyslipoproteinaemia;
  - obesity (body mass index over 30 kg/m^2);
  - hypertension;
  - migraine;
  - valvular heart disease;

- atrial fibrillation;
- a positive family history (arterial thrombosis in a sibling or parent at a relatively young age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before making a decision regarding the use of a hormonal contraceptive.

- Other diseases that have been associated with adverse circulatory events, including diabetes mellitus, systemic lupus erythematosus, haemolytic-uraemic syndrome, chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and sickle cell anaemia.

- The increased risk of thromboembolism in the puerperium must be considered (for information on "Pregnancy and lactation", see section 4.6).

- An increase in the frequency or severity of migraine whilst using Diane-35 (which may be prodromal for a cerebrovascular event) can be a reason for immediate discontinuation of Diane-35.

Women using Diane-35 should be specifically instructed to contact their physician if possible symptoms of thrombosis occur. Diane-35 must be discontinued if thrombosis is suspected or confirmed. Due to the teratogenicity of anticoagulants (coumarins), appropriate methods of contraception should be used.

Arterial thromboembolic events can be life-threatening or have a fatal outcome.
It should be noted that the risk of thrombosis may be higher due to synergistic effects of individual risk factors, when a combination of these risk factors is present, or if any marked risk factor occurs in the user.
Diane-35 should not be prescribed in the event of a negative benefit/risk assessment (see section 4.3).

Tumours
The most important risk factor for cervical cancer is persistent infection with the human papillomavirus (HPV). Some epidemiological studies have indicated that long-term use of oestrogen-progestogen combinations might further increase this risk. However, there is some controversy about the extent to which these findings are attributable to confounding factors, such as cervical screening and sexual behaviour, including the use of barrier methods.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer in women who are currently using oestrogen-progestogen combinations. The excess risk gradually disappears during the course of the 10 years after cessation of oestrogen-progestogen combinations. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent users of oestrogen-progestogen combinations 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 users, the biological effects of these medicines or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported, possibly leading to life-threatening intra-abdominal haemorrhage, after the use of hormonal substances, such as those contained in Diane-35. If non-specific upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential diagnosis.

Malignant tumours can be life-threatening or have a fatal outcome.

Meningioma
The occurrence of meningiomas (single and multiple) has been reported in association with the use of cyproterone acetate, in particular at high doses of 25 mg a day and above as well as in the event of

prolonged use (see section 5.1). If a patient is diagnosed with meningioma, treatment with all cyproterone-containing products, including Diane-35, must be stopped as a precaution.

Other disorders
Women with hypertriglyceridaemia, or a positive family history thereof, may be at increased risk of developing pancreatitis if they take oestrogen-progestogen combinations.

Although a slight increase in blood pressure has been reported in many women taking oestrogen-progestogen combinations (such as, for example, COCs or Diane-35), clinically significant increases in blood pressure are rare. However, if persistent, clinically relevant hypertension develops during use of Diane-35, the woman should stop taking Diane-35 and the hypertension should be treated. If it seems appropriate, the woman can resume taking Diane-35 as soon as blood pressure values have normalised with antihypertensive therapy.

The following disorders are reported to occur or deteriorate during both pregnancy and the use of oestrogen-progestogen combinations. However, no connection with oestrogen-progestogen combinations could be demonstrated: cholestatic jaundice and/or pruritus; gallstones; porphyria; systemic lupus erythematosus; haemolytic-uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss, epilepsy.

Exogenously administered oestrogens may precipitate or exacerbate symptoms of hereditary and acquired angioedema.

Acute or chronic liver dysfunction may necessitate discontinuation of Diane-35 use until liver function values have normalised. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus that occurred during a previous pregnancy or during previous use of steroid sex hormones also requires discontinuation of Diane-35.

Although oestrogen-progestogen combinations can have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence of any need to change the therapeutic regimen in diabetics using low-dose oestrogen-progestogen combinations (with < 0.05 mg ethinylestradiol). However, diabetics must be carefully monitored whilst they are taking Diane-35.

Crohn's disease and ulcerative colitis have been associated with the use of oestrogen-progestogen combinations.

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their doctor in the event of mood changes or depressive symptoms, including shortly after initiating treatment.

Chloasma can occur uncommonly, especially in women with a history of chloasma gravidarum. Women with this predisposition should not directly expose themselves to the sun or ultraviolet light whilst taking Diane-35.

Reduced efficacy
The contraceptive efficacy of Diane-35 may be reduced in the event of e.g. missed tablets (Section 4.2), gastrointestinal disturbances (Section 4.2) or certain concomitant medication (Section 4.5).

Irregular bleeding
With all preparations containing an oestrogen/progestogen combination, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first few months of use.

It is possible that withdrawal bleeding may fail to occur in some users during the tablet-free interval (7-day break between tablet-taking). Pregnancy is unlikely if Diane-35 has been taken as described in section 4.2. However, if Diane-35 has not been taken as prescribed prior to the first absence of

withdrawal bleeding or if breakthrough bleeding has failed to occur for a second time, pregnancy must be excluded before Diane-35 use is continued.

Diane-35 contains 31 mg lactose monohydrate and 19 mg sucrose per tablet. Patients with rare hereditary problems of galactose or fructose intolerance, lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not take Diane-35.

4.5 Interaction with other medicaments and other forms of interaction

Note: For each co-prescribed medicinal product, the Summary of Product Characteristics should be reviewed for possible interactions.

Effect of other medicinal products on Diane-35
Interactions can occur with active substances that induce microsomal enzymes, which may increase the clearance of sex hormones and lead to breakthrough bleeding and/or contraceptive failure.

Enzyme induction may be observed within a few days of treatment. The maximum enzyme-induced effect is normally observed within a few weeks. The enzyme-induced effect may last for up to 4 weeks after treatment is finished.

Women treated with any such medicinal products should use a barrier method in addition to Diane-35 during this time. The barrier method should be used throughout the period whilst taking the co-medication and for a further 28 days thereafter. If use of the additional barrier method runs beyond the end of the tablets in the Diane-35 pack, tablet-taking should continue from the next Diane-35 pack without the usual 7-day interval.

Substances that increase the clearance of Diane-35 (reduced effectiveness of Diane-35 due to enzyme induction):
e.g. barbiturates, rifampicin and antiepileptic drugs (such as barbexaclone, carbamazepine, phenytoin, primidone) and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort (Hypericum).

Substances with various effects on the clearance of Diane-35
During concomitant use with Diane-35, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can lead to an increase or decrease in the plasma concentrations of oestrogen or progestogen. These changes may be clinically relevant in some cases.

Substances that reduce the clearance of oestrogen-progestogen combinations (enzyme inhibitors):
The clinical relevance of potential interactions with enzyme inhibitors is unknown.

The concomitant administration of potent CYP3A4 inhibitors can increase the plasma concentration of oestrogens or progestogens or both.

At doses of 60 to 120 mg/day, etoricoxib has been shown to increase the plasma concentrations of ethinylestradiol 1.4 to 1.6-fold when taken at the same time as a hormonal contraceptive containing 0.035 mg of ethinylestradiol.

Effect of oestrogen-progestogen combinations on other medicinal products
Oestrogen-progestogen combinations such as Diane-35 can affect the metabolism of certain other medicinal products. Accordingly, plasma levels and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

The requirement for antidiabetics can change as a result of the effect on glucose tolerance.

Clinical data suggest that ethinylestradiol inhibits the clearance of CYP1A2 substrates, thereby leading to a slight (e.g. theophylline) or moderate (e.g. tizanidine) rise in the plasma concentration thereof.

Pharmacodynamic interactions
During clinical trials with patients treated for hepatitis C virus infections (HCV) with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see section 4.3).

Diane-35 users must therefore switch to an alternative method of contraception (e.g. progestogen-only contraception or non-hormonal barrier methods) prior to starting therapy with this combination of medicinal products. Diane-35 can be restarted 2 weeks following completion of treatment with this medicinal product combination.

Other interactions

Laboratory tests
The use of preparations such as Diane-35 may influence the results of certain laboratory tests. This includes biochemical parameters of hepatic, thyroid, adrenal and renal function, as well as the plasma levels of (carrier) proteins, e.g. corticosteroid-binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism, blood coagulation and fibrinolysis. However, these changes generally remain within the normal range.
Note
Diane-35 may not be used with an additional hormonal contraceptive; such medicinal products have to be discontinued prior to starting treatment with Diane-35 (for this, see also 4.2).

4.6 Pregnancy and lactation

Pregnancy
Pregnancy must be excluded. Diane-35 is contraindicated during pregnancy. If pregnancy occurs during medication with Diane-35, the preparation is to be withdrawn immediately. Previous use of Diane-35, however, is not a reason for a termination of pregnancy.

Breastfeeding
Diane-35 is contraindicated during breastfeeding.
Cyproterone acetate is transferred into the milk of lactating women. Approximately 0.2% of the maternal dose can be transferred to the breast-fed infant, which corresponds to a dose of approximately 1 µg/kg.

During lactation, approximately 0.02% of the daily maternal dose of ethinyl estradiol can be absorbed by the neonate via breast milk.

4.7 Effects on ability to drive or use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

4.8.1. Summary of the safety profile

The most commonly reported undesirable effects associated with Diane-35 are nausea, abdominal pain, weight gain, headache, depression, mood swings, breast pain and breast tenderness. They occur in $\geq$ 1% to < 10% of all users.

There is an increased risk of thromboembolism in all women who use Diane-35 (see section 4.4).

4.8.2 Table of undesirable effects

Side effects that have been reported in users of Diane-35, but for which the association has been neither confirmed nor refuted, are:

System organ class (MedDRA)	**Frequency of undesired effects**			
	Common ≥ 1/100 to < 1/10	**Uncommon < 1/100 to ≥ 1/1,000**	**Rare ≥ 1/10,000 to < 1/1,000)**	**Not known** Frequency cannot be estimated from the available data
Eye disorders			contact lens intolerance	
Vascular disorders			thromboembolism	Increase in blood pressure
Gastrointestinal disorders	nausea, abdominal pain	vomiting, diarrhoea		
Immune system disorders			hypersensitivity reactions	Exacerbation of the symptoms of hereditary and acquired angioedema
Investigations	weight increase		weight decrease	
Metabolism and nutrition disorders		fluid retention		
Nervous system disorders	headache	migraine		
Psychiatric disorders	depressive mood, mood altered	Influence on libido		
Reproductive system and breast disorders	breast pain, breast tenderness intermenstrual	breast hypertrophy	mammary gland secretion, vaginal discharge	
Skin and subcutaneous tissue disorders		rash, urticaria, chloasma	erythema nodosum, erythema multiforme	

4.8.3 Description of selected undesirable effects

An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischaemic attacks, venous thrombosis and pulmonary embolism, has been observed in women using oestrogen-progestogen combinations, and these are discussed in more detail in section 4.4.

The following serious adverse reactions observed in women using oestrogen-progestogen combinations have been reported and are explained in section 4.4 "Special warnings and precautions for use":

- Venous thromboembolism,
- Arterial thromboembolism,
- Hypertension,
- Hepatic tumours (benign or malignant),
- Occurrence or deterioration of conditions which have not been conclusively proven to be associated with the use of combined oestrogen-progestogen contraceptives: Crohn's disease, ulcerative colitis, epilepsy, uterine myomas, porphyria, systemic lupus erythematosus, pemphigoid gestationis, Sydenham's chorea, haemolytic-uraemic syndrome, cholestatic jaundice,
- Chloasma,
- Acute or chronic liver dysfunction may necessitate the discontinuation of oestrogen-progestogen combinations until liver function markers return to normal.

The frequency with which breast cancer is diagnosed is slightly increased in users of oestrogen-progestogen combinations. As breast cancer rarely occurs in women below 40 years of age, the additional risk of developing breast cancer is small in relation to the overall risk. Causality with the use of oestrogen-progestogen combinations is not known. For more information, see sections 4.3 and 4.4.

If symptoms have significantly worsened recently in women who suffer from hirsutism, the causes of this (androgen-producing tumour, enzyme defect in the adrenal cortex) must be clarified by differential diagnosis.

Interactions
Intermenstrual bleeding and/or contraceptive ineffectiveness may occur as a result of interactions between oestrogen-progestogen combinations and other medicinal products (enzyme-inducing medicines) (see section 4.5).

Effect on clinical chemistry normal values
The erythrocyte sedimentation rate can increase without a disease being present. There have also been reports of increased serum copper and serum iron levels, as well as alkaline leukocyte phosphatase activity.

Other metabolic functions
Infrequent disturbances in folic acid and tryptophan metabolism may occur.

Taken regularly, Diane-35 has a contraceptive effect due to its composition. The irregular intake of Diane-35 can lead to irregular menstrual cycles. The regular intake of Diane-35 is very important in preventing both cycle irregularities and pregnancy (because of a possible effect of cyproterone acetate on a developing child).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Bundesinstitut für Arzneimittel und Medizinprodukte (= Federal Institute for Drugs and Medical Devices), Department of Pharmacovigilance, Kurt-Georg-Kiesinger-Allee 3, D-53175 Bonn, website: www.bfarm.de.

4.9 Overdose

There are no data available on overdose in humans. Based on the general data gathered with combined oral contraceptives, symptoms that can possibly occur are: nausea, vomiting and unexpected bleeding. If they accidentally take this medicinal product, vaginal bleeding may even occur in girls who have not yet had their first period. There are no antidotes, and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiandrogens and estrogens
ATC code: G03HB

Hair follicles and sebaceous glands are androgen sensitive. Acne and seborrhoea are due, in part, to a sebaceous gland dysfunction, caused by increased peripheral sensitivity or raised androgen plasma levels. Both active ingredients in Diane-35 have a positive therapeutic effect. Cyproterone acetate competitively displaces androgens in the effector organ, thus cancelling the androgenic effect. The plasma androgen concentration is then reduced by an antigonadotropic effect. Ethinyl estradiol intensifies this effect, which leads to an up-regulation of sex–hormone binding globulin (SHBG). Plasma free androgen levels are reduced. Acne efflorescences generally heal after 3 to 4 months when treated with Diane-35. Oiliness of the skin and hair disappears first. Androgen-dependent hair loss is also reduced. It has to be pointed out that the effect is slow when treating female hirsutism. It may take several months to show effects.

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Cyproterone acetate is also a potent progestogen, which possesses a contraceptive effect when used in combination with ethinyl estradiol. It rests on the interaction of central and peripheral mechanisms, of which ovulation inhibition and changes to cervical secretion have to be considered the most important. Moreover, the morphological and enzymatic changes in the endometrium provide extremely unfavourable conditions for nidation.

Contraceptive protection begins with the first day of use.

Meningioma
Based on results from a French epidemiological cohort study, a cumulative dose-dependent association between cyproterone acetate and meningioma has been observed. This study was based on data from the French Health insurance (CNAM) and included a population of 253,777 women using 50 - 100 mg cyproterone acetate. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose cyproterone acetate (cumulative dose ≥ 3 g) and women who were merely slightly exposed to cyproterone acetate (cumulative dose < 3 g). A cumulative dose-response relationship was demonstrated.

Cumulative dose of cyproterone acetate	Incidence rate (in patient years)	HR_{adj} (95% CI)[a]
Slightly exposed (< 3 g)	4.5/100,000	Ref.
Exposed to ≥ 3 g	23.8/100,000	6.6 [4.0-11.1]
12 to 36 g	26/100,000	6.4 [3.6-11.5]
36 to 60 g	54.4/100,000	11.3 [5.8-22.2]
more than 60 g	129.1/100,000	21.7 [10.8-43.5]

[a] Adjusted based on age as a time-dependent variable and oestrogen at inclusion

A cumulative dose of 12 g for example can correspond with one year of treatment with 50 mg/day for 20 days a month.

5.2 Pharmacokinetic properties

Cyproterone acetate (CPA))

Absorption
Following oral administration CPA is completely absorbed in a wide dose range. The ingestion of Diane-35 effects a maximum serum level of 15 ng of CPA/mL at 1.6 hours.
The absolute bioavailability of CPA is 88% of dose. The relative bioavailability of CPA from Diane-35 was 109%, when compared to an aqueous microcrystal suspension,

Distribution
CPA is present in serum almost exclusively in protein-bound form. About 3.5 - 4.0% of total CPA levels are present unbound and the remainder is bound to albumin. Since CPA binding to sex hormone binding globulin (SHBG) is non-specific, changes in SHBG levels caused by ethinyl estradiol do not affect the pharmacokinetics of CPA.

Metabolism
CPA is metabolised by various pathways, including hydroxylation and conjugation steps. The main metabolite in human plasma is the 15β-hydroxy derivative.

Elimination
Serum concentrations decrease in two disposition phases characterised by half-lives of 0.8 hours and 2.3 days. The total clearance of CPA from serum is 3.6 $mL/min^{-1}/kg^{-1}$.
Some CPA dose parts are excreted unchanged with the bile fluid. Most of the dose is excreted in form of metabolites at a urinary to biliary ratio of 3:7 with a half-life of 1.9 days. Metabolites from plasma are eliminated at a similar rate (half-life of 1.7 days).

Steady-state conditions
That CPA accumulates during one treatment cycle is to be expected by virtue of the long half-life of the terminal disposition phase of CPA from serum and the daily intake. Mean maximum drug serum levels increase from 15 ng/mL (day 1) to 21 ng/mL and 24 ng/mL at the end of the treatment cycles 1 and 3 respectively. Steady-state conditions are reached after approximately 10 days. During long-term treatment, CPA accumulates over treatment cycles by about a factor of 2 – 2.5.

Smoking does not affect the pharmacokinetics of CPA.

Ethinyl estradiol (EE_2)

Absorption
Orally administered EE_2 is absorbed rapidly and completely. After a single ingestion of Diane-35, maximum EE_2 serum levels of about 80 pg/mL are reached at 1.7 hours.
The relative bioavailability of EE_2 from Diane-35, with reference to an aqueous microcrystalline suspension, was almost complete.

Distribution
An apparent distribution volume of approximately 5 L/kg was determined for EE_2.

EE_2 is highly but non-specifically bound to serum albumin. 2% of the EE_2 levels are present unbound.

The bioavailability of EE_2 can be changed in both directions by other active substances. There is, however, no interaction with high doses of vitamin C. EE_2 induces the hepatic synthesis of SHBG and corticosteroid-binding globulin (CBG) during continuous use. The extent of SHBG induction is dependent, however, on the chemical structure and dose of the co-administered progestogen. During treatment with Diane-35, an increase was observed in the SHBG serum levels from approximately 100 nmol/L to 300 nmol/L and in the CBG serum levels from about 50 ug/mL to 95 pg/mL.

Metabolism
EE_2 is metabolised during absorption and the first liver passage resulting in a reduced absolute and variable oral bioavailability.
For EE_2, the metabolic clearance rate from plasma was determined to be about 5 mL/min/kg.

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.

Elimination
The EE_2 plasma levels decrease in two phases characterised by half-lives of 1 - 2 hours and about 20 hours. For analytical reasons, these parameters can only be calculated for higher dosages.

Unchanged EE_2 is not eliminated. The metabolites of EE_2 are eliminated at a urinary to biliary ratio of 4:6 with a half-life of about 1 day.

Steady-state conditions
According to the half-life of the terminal disposition phase of EE_2 from serum and the daily ingestion, steady state levels are reached after 3 - 4 days and are higher by 30–40% as compared to a single dose.

5.3 Preclinical safety data

Ethinyl estradiol

The toxicity profile of ethinyl estradiol is well known. There are no preclinical safety data, which reveal relevant risks for humans and are not already included in other sections of the summary of product characteristics.

Cyproterone acetate

Systemic toxicity
Preclinical data reveal no specific risk for humans using Diane-35 based on conventional studies of repeated dose toxicity.

Reproductive toxicity, teratogenicity
The administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs causes signs of feminisation in male foetuses after high doses. Observation of male neonates who had been exposed in utero to cyproterone acetate did not show any signs of feminisation. Nevertheless, pregnancy is a contraindication for the use of Diane-35. Investigations into embryo-foetal development toxicity using the combination of both active ingredients showed no potential indicative of a teratogenic effect following treatment during organogenesis (end of treatment preceded the completed differentiation of the external genitalia) that exceeded the known effects on the differentiation of the male genital tract.

Genotoxicity, carcinogenicity
Recognised first-line tests of genotoxicity gave no indication of a mutagenic effect when conducted with cyproterone acetate. In further investigations, cyproterone acetate, however, was capable of producing adducts with DNA (and an increase in DNA repair activity) in liver cells from rats, monkeys and humans.

This DNA-adduct formation occurred under conditions of exposure 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.

The clinical significance of these findings is currently uncertain. Clinical experience to date would not support an increased incidence of hepatic tumours in man.

Investigations into the tumourigenicity of cyproterone acetate in rodents did not reveal any results that fundamentally differed from those obtained with other steroid hormones. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissue and tumours.
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 doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
lactose monohydrate
maize starch
polyvidone K25
talc
magnesium stearate

Coating:
sucrose
polyvidone K90
macrogol 6000
calcium carbonate (E 170)
talc
glycerol 85 % (E 422)
titanium dioxide (E 171)
iron(lll) hydroxide/oxide x H_20 (E 172)
montanglycol wax, Wax E.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

PVC/aluminium blister of

21 coated tablets
3x21 coated tablets
6x21 coated tablets

in calendar packs

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

347.01.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the first authorisation: 1 October 1985
Date of renewal: 23 January 2002

10. DATE OF REVISION OF THE TEXT

October 2022

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.