SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

DIANE®-35 0,035 mg/2,0 mg coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

21 hormone-containing beige coated tablets:
Each coated tablet contains ethinylestradiol 0,035 mg and cyproterone acetate 2 mg
Contains sugar (19 mg sucrose and 31 mg lactose monohydrate)

7 hormone-free larger white coated tablets.
Contains sugar (34 mg sucrose and 48 mg lactose monohydrate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablets
The hormone-containing tablet is small beige, round with convex faces
The hormone-free tablet is large white, round with convex faces

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age.
This includes patients with polycystic ovary syndrome requiring treatment of these symptoms.
For the treatment of acne, DIANE-35 should be used when topical therapy or systemic antibiotic treatments are not considered appropriate.
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

Posology

How to take DIANE-35

DIANE-35 is to be taken regularly in order to achieve the therapeutic efficacy and the required contraceptive protection. Previously used hormonal contraception should be discontinued. The dose regimen of DIANE-35 is similar to the usual regimen of most of the combined oral contraceptives. Thus, the same administration rules must be considered. Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1 % per year. The irregular intake of DIANE-35 can lead to intermenstrual bleedings and could deteriorate the therapeutic and contraceptive reliability. Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. Tablet-taking is continuous. One tablet is to be taken daily for 28 consecutive days.

Each subsequent pack is started the day after the last tablet of the previous pack. Withdrawal bleeding usually starts on day 2-3 after starting the hormone-free larger white coated tablets 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 women's natural cycle (i.e. the first day of her menstrual bleeding), but during the first cycle an additional barrier method is recommended for the first 14 days The first tablet should be taken from the starter section of the calendar pack by selecting the appropriate tablet for that day of the week (e.g. "Mon" for Monday).

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

The woman should start with DIANE-35 on the day after the last hormone-containing tablet of her previous oral contraceptive. In case a vaginal ring or transdermal patch has been used, the woman should start using DIANE-35 on the day of removal of the last ring or patch of a cycle pack.

- 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 during the first cycle an additional barrier method is recommended for the first 14 days of tablet-taking.

- Following first trimester abortion

The woman may start immediately, but during the first cycle an additional barrier method is recommended for the first 14 days of tablet-taking.

- Following delivery or second trimester abortion

For breastfeeding women see section 4.6.
Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion, but during the first cycle an additional barrier method is recommended for the first 14 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of DIANE-35 or the woman has to wait for her first menstrual period.

Management of missed tablets

Missed hormone-free larger white coated tablets can be disregarded. However, they should be discarded to avoid unintentionally prolonging the hormone-free larger white tablet phase.
The following advice only refers to **missed hormone-containing beige** coated tablets:
If the user is **less than 12 hours** late in taking any hormone-containing 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 hormone-containing tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:
1. tablet-taking must never be discontinued for longer than 7 days.
2. 7 days of uninterrupted hormone-containing tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis

If a hormone-containing tablet has been missed for more than 12 hours, 7 days of additional barrier methods are required.
If the woman missed tablets and subsequently has no withdrawal bleed in the hormone-free larger white coated tablet phase, the possibility of a pregnancy should be considered.

How to proceed in the case of intermenstrual bleeding

If an intermenstrual bleeding occurs during the 3 weeks in which the beige tablets are being taken, their use should not be interrupted. A slight bleeding (spotting) will usually stop spontaneously. However, if the bleeding is heavy, similar to a menstrual bleeding, then a thorough examination is indicated to exclude organic factors.

If bleeding fails to occur while the tablets from the starter section are being taken, tablet-taking must provisionally be stopped, and the doctor must be consulted.

Advice in the case of gastrointestinal disturbances

In case of severe gastro-intestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.
If vomiting occurs within 3-4 hours after taking a hormone-containing beige coated tablet, 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 androgenisation and their response to treatment. In general, treatment should be carried out over several months. Time to relief of symptoms is at least 3 months. Acne and seborrhoea 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 venous thromboembolism should be considered (see section 4.4).

Method of administration

Oral use

4.3. Contraindications

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

- Hypersensitivity to the active substances or to any of the excipients (see section 6.1).
- Venous thrombosis present or in history (deep venous thrombosis, pulmonary embolism).
- Arterial thrombosis present or in history (e.g. myocardial infarction) or prodromal conditions (e.g. angina pectoris and transient ischaemic attack).
- Presence or history of cerebrovascular accident
- History of migraine with focal neurological symptoms.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis (see section 4.4) such as:
    - diabetes mellitus with vascular symptoms

  - severe hypertension
  - severe dyslipoproteinaemia
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as activated protein C (APC) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- 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 section 4.5)
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Concomitant use with another hormonal contraceptive (see section 4.1).
- Known or suspected pregnancy.
- Lactation

DIANE-35 is not for use in men.

4.4. Special warnings and precautions for use

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

Circulatory disorders

The use of DIANE-35 carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman starts DIANE-35 or when restarting or switching after a pill-free interval of at least a month. Venous thromboembolism can be fatal in 1-2% of cases.

Epidemiological studies have shown that the incidence of VTE is 1,5 to 2 times higher in users of DIANE-35 than in users of levonorgestrel-containing combined oral contraceptives (COCs) 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 accidents 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 medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle-cell disease.

The increased risk of thromboembolism in the puerperium must be considered (see section 4.6).

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, hyperhomocysteinaemia, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).

Women using DIANE-35 should be specifically pointed out to contact their medical practitioner in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, DIANE-35 use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy.

Arterial thromboembolic events may be life-threatening or may 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 human papilloma virus infection. Some epidemiological studies have indicated that long-term use of combined oral contraceptives may further contribute to an increased risk of cervical cancer but the extent to which this finding is attributable to confounding effects (e.g. cervical screening and sexual behaviour including use of barrier contraceptives) continues to be discussed.

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 combined oral contraceptives. The excess risk gradually disappears during the course of the 10 years after cessation of combined oral contraceptives use.

Benign liver tumours and malignant liver tumours have been reported in users of combined oral contraceptives possibly leading to life-threatening intra-abdominal haemorrhage. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking DIANE-35.

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

Other disorders

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using combined oral contraceptives.

Small increases in blood pressure have been reported in many women taking combined oral contraceptives which contains ethinylestradiol. However, clinically relevant increases may also occur. If a sustained clinically significant hypertension develops during the use of DIANE-35, then it is prudent for the medical practitioner to withdraw DIANE-35 and treat the hypertension.

The occurrence or deterioration of the following conditions have been reported to occur or deteriorate with combined oral contraceptive use: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens such as contained in DIANE-35 may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of DIANE-35. Recurrence of cholestatic jaundice which first occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of DIANE-35.

DIANE-35 may have an effect on peripheral insulin resistance and glucose tolerance, hence, diabetic women should be carefully monitored while taking DIANE-35.

Crohn's disease and ulcerative colitis have been associated with combined oral contraceptive use.

Chloasma may 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 DIANE-35.

Depressed mood and depression are well-known undesirable effects oof hormonal contraceptive use (see section 4.8). Depression can be severe and is a well-known risk factor for suicidal behaviour and suicide.

Women should be advised to contact that medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of DIANE-35 use, guided by the Contraindications and Warnings (see section 4.3 and 4.4), 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 a combined oral contraceptive. 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, breasts, abdomen and pelvic organs, including cervical cytology.

Women should be advised that DIANE-35 does not protect against HIV infections (AIDS) and other sexually transmitted diseases (STDs). Women should be advised that additional barrier contraceptive measures are needed to prevent transmission of STDs and HIV.

Reduced efficacy

The contraceptive effect of DIANE-35 may be reduced in the event of missed hormone-containing beige coated tablets, gastro-intestinal disturbances (see section 4.2) during hormone-containing beige coated tablet taking or concomitant medication (see section 4.5).

Reduced cycle control

Irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. In some women withdrawal bleeding may not occur during the hormone-free larger white coated tablet phase. If DIANE-35 has been taken according to the directions described in section 4.2, it is unlikely that the woman is pregnant. However, if DIANE-35 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 DIANE-35 use is continued.

4.5. Interaction with other medicines and other forms of interaction

Note: The Professional Information on concomitant medications should be consulted to identify potential interactions.

Effects of other medicines on DIANE-35

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

Enzyme induction can be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of medicine therapy, enzyme induction may be sustained for about 4 weeks.

Women on treatment with any of these medicines 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 medicine administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the hormone-containing beige coated tablets in

the DIANE-35 pack, the hormone-free larger white coated tablets should be omitted and the next pack started.

Substances increasing the clearance of DIANE-35 (diminished efficacy 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 combined oral contraceptives, 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 DIANE-35 on other medicines

Estrogen/progestogen combinations like DIANE-35 may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) 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 interactions

Co-administration of ethinylestradiol-containing medicines such as DIANE-35 with direct-acting antiviral (DAA) medicines 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 section 4.3).

Other forms of interactions

Laboratory tests

The use of contraceptive steroids 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.

4.6. Pregnancy and lactation

Pregnancy

Use of DIANE-35 is contraindicated in pregnancy (see section 4.3). If pregnancy occurs during treatment with DIANE-35, further intake must be stopped (see section 5.3)

Lactation

The administration of DIANE-35 is contraindicated during lactation (see section 4.3). Cyproterone acetate is transferred into the milk of lactating women.

4.7. Effects on ability to drive and use machines

None.

4.8. 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.

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

Tabulated summary of adverse reactions
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) and rare (≥ 1/10 000 to < 1/1 000).

System Organ Class	**Common (≥1/100 to < 1/10)**	**Uncommon (≥1/1 000 to < 1/100)**	**Rare (≥1/10 000 to < 1/1 000)**
Eye disorders			Contact lens intolerance
Gastrointestinal disorders	Nausea Abdominal pain	Vomiting Diarrhoea	
Immune system disorders			Hypersensitivity
Investigations	Increased weight		Decreased weight
Metabolism and nutrition disorders		Fluid retention	
Nervous system disorders	Headache	Migraine	
Psychiatric disorders	Depressed mood Altered mood	Decreased libido	Increased libido
Reproductive system and breast disorders	Brest 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.

Post-marketing side effects

Depression can be severe and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact that medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

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 4.3 and 4.4).

Tumours

- The frequency of diagnosis of breast cancer is very slightly increased among oral contraceptive 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 combined oral contraceptive use is unknown.
- Liver tumours (benign and malignant)

Other conditions

- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Cerebrovascular accidents
- Increased risk of pancreatitis when using combined oral contraceptives (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; haemolytic 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 medicines (enzyme inducers) with oral contraceptives (see section 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antiandrogens and estrogens
ATC code: G03HB

The substance cyproterone acetate contained In DIANE-35 blocks the effect of endogenously produced and exogenously administered androgens at the target organs by means of competitive inhibition. The stimulating effect of male sex hormones on androgen-dependent structures and functions is weakened or abolished by cyproterone acetate.

Excessive sebaceous gland function is decreased.

Apart from the described anti-androgen effect, cyproterone acetate also has a progestational action. The ethinylestradiol in the combination inhibits ovulation and changes the cervical mucus and the endometrium rendering them unfavourable for sperm penetration and nidation of a fertilised ovum, respectively.

5.2. Pharmacokinetic properties

Cyproterone acetate

Absorption

Orally administered cyproterone acetate is rapidly and completely absorbed. Peak serum concentrations of 15 ng/ml are reached at about 1,6 hours after single ingestion. Bioavailability is about 88 %.

Distribution

Cyproterone acetate is almost exclusively bound to serum albumin. Only 3,5 – 4,0 % of the total serum 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 metabolised. 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 characterised by half-lives of about 0,8 h and about 2,3 – 3,3 days. Cyproterone acetate is partly excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1:2. The half-life of metabolite excretion is about 1,8 days.

Steady-state conditions

Cyproterone acetate pharmacokinetics are not influenced by SHBG levels. Following daily ingestion 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 metabolised 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 pre-systemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The clearance rate was reported to be about 2,3 - 7 ml/min/kg.

Elimination

Ethinylestradiol serum levels decrease in two disposition phases characterised by half-lives of about 1 hour and 10 - 20 hours, respectively. Unchanged ethinylestradiol 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 levels are higher by 60 % as compared to single dose

5.3. Preclinical safety data

Administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs (after approximately day 45 of gravidity) could lead to signs of feminisation in male foetuses following higher doses. Observation of male newborn children who had been exposed in utero to cyproterone acetate did not show any signs of feminisation. However, pregnancy is a contra-indication for the use of DIANE-35.

Recognised first-line tests of genotoxicity gave negative results when conducted with cyproterone acetate. However, there is some evidence of genotoxicity as 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. This DNA adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. One in vivo consequence of cyproterone acetate treatment was the increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats.

The clinical relevance of these findings and how these findings relate to the risk of developing benign and malignant liver tumours in humans is presently unknown. Clinical experience to date would not support an increased incidence of hepatic tumours in humans. 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 such as the substances contained in DIANE-35 can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARAMCEUTICAL PARTICULARS

6.1. List of excipients

Calcium carbonate precipitate
Ferric oxide yellow pigment
Glycerol 85 %
Lactose monohydrate
Macrogol 6000
Magnesium stearate
Maize starch
Montanglycol wax
Povidone 25
Povidone 700 000
Sucrose
Talc
Titanium dioxide

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store at or below 30 °C.
Protect from light

6.5. Nature and content of container

PVC/PE.EVOH.PE/PCTFE/aluminium blisters of 28 tablets.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
ISANDO
1609

8. REGISTRATION NUMBER

V/21.8.2/300

9. DATE OF FIRST AUTHORISATION

22 September 1988

10. DATE OF REVISION OF THE TEXT

21 July 2022