

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DIANE® 35 ED cyproterone acetate 2 mg, ethinylestradiol 35 micrograms, film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each active beige tablet contains:

Cyproterone acetate 2 mg
Ethinylestradiol 35 micrograms

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

21 beige, round active tablets.

7 white, round placebo tablets.

All tablets have a lustrous sugar coating. Tablets cannot be halved.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of signs of androgenisation in women, such as severe acne (involving inflammation or nodularity or risk of scarring) where prolonged oral antibiotics or local treatment alone has not been successful, or idiopathic hirsutism of mild to moderate degree.

DIANE-35 ED will also provide effective oral contraception in this patient group. It should not be used in combination with other hormonal contraceptives (see CONTRAINDICATIONS).

If the hirsutism has only recently appeared or has lately intensified to a considerable extent the cause (androgen-producing tumour or an adrenal-enzyme defect) must be clarified by differential diagnosis.

4.2 Dose and method of administration

DIANE-35 ED is to be taken regularly in order to achieve the therapeutic efficacy and the required contraceptive protection. Previously used hormonal contraception should be discontinued. The dose regimen of DIANE-35 ED is similar to the usual regimen of most combined oral contraceptives. Thus, the same administration rules must be considered. Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1 % per year.

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

Length of Use

Treatment will probably need to be continued for about 6 months and probably much longer to gain an acceptable therapeutic effect, especially if Diane-35 ED is being used for the treatment of excessive hair. The length of use depends on the severity of the symptoms of androgenisation and their response to treatment. Acne and seborrhoea usually respond sooner than hirsutism. The need to continue treatment should be evaluated periodically by the treating doctor. It is possible that the original condition will recur once treatment with Diane-35 ED is stopped.

Diane-35 ED should be withdrawn 3 to 4 cycles after the treated condition has completely resolved. Repeat course of Diane-35 ED may be given if the androgen-dependent condition(s) recur. In case of a restart of DIANE-35 ED (following a 4 week or greater pill free interval), the increased risk of VTE should be considered (see Warnings and Precautions).

How to take DIANE-35 ED

Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. One tablet is to be taken daily. Do not halve the tablet. Each subsequent pack is started immediately following the previous pack. Withdrawal bleeding should usually occur on day 2 to 3 after the last beige active tablet is taken and may not have finished before the next pack is started.

How to start DIANE-35 ED

- **No preceding hormonal contraceptive use (in the past month)**

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). The first tablet should be selected from the red starting section of the pack.

Additional non-hormonal contraceptive methods must be used for the first 14 days of tablet-taking.

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

The woman should start DIANE-35 ED in the red section on the day after the last active tablet of her previous COC.

In case a vaginal ring or transdermal patch has been used, the woman should start taking DIANE-35 ED preferably on the day of removal.

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

The woman may switch from the minipill on any day, from an implant or the IUS on the day of its removal, or from an injectable when the next injection would be due, but in all of these cases she should be advised to additionally use a non-hormonal method of contraception for the first 14 days of tablet-taking.

- **Following First-Trimester Abortion**

The woman may start immediately. Additional non-hormonal contraceptive methods are necessary for the first 14 days of tablet-taking.

- **Following Delivery or Second-Trimester Abortion**

For breast-feeding woman, see PRECAUTIONS.

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

When starting later, the woman should be advised to additionally use a barrier method 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 ED use or the woman has to wait for her first menstrual period.

Management of Missed Tablets

Errors in taking the white placebo tablets contained in DIANE-35 ED can be ignored. However they should be discarded to avoid unintentionally prolonging the placebo tablet phase. The following advice only refers to missed beige active tablets (rows 1 -3 of the blister):

If the woman is **less than 12 hours** late in taking any beige active tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If the woman is **more than 12 hours** late in taking any beige active tablet, contraceptive protection may be reduced.

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

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

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

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

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

Extra Contraceptive Precautions

When you need extra contraceptive precautions, either:

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

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

The 7 Day Rule

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

Advice in Case of Gastrointestinal Disturbances

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

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

How to Shift Periods or How to Delay a Period

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

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming tablet-free interval or omit the white placebo tablets in DIANE-35 ED by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and

will experience breakthrough-bleeding and spotting during the second pack (just as when delaying a period).

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.

- Presence or risk of venous thromboembolism (VTE) (see 4.4 Special warnings and precautions for use)
 - Current VTE (on anticoagulants) or history of deep venous thrombosis [DVT] or pulmonary embolism [PE]
 - Known hereditary or acquired predisposition for VTE, such as APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
 - Major surgery with prolonged immobilisation
 - A high risk of VTE due to the presence of multiple risk factors
- Presence or risk of arterial thromboembolism (ATE) (see 4.4 Special warnings and precautions for use)
 - Current ATE or history of ATE (e.g. myocardial infarction [MI] or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA])
 - Known hereditary or acquired predisposition for ATE, such as hyperhomocysteinaemia and antiphospholipid-antibodies (e.g. anticardiolipin-antibodies and lupus anticoagulant)
 - History of migraine with focal neurological symptoms
 - A high risk of ATE due to multiple risk factors or to the presence of one serious risk factor such as:
 - diabetes mellitus with vascular symptoms
 - severe hypertension
 - severe dyslipoproteinaemia
- 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 INTERACTIONS)
- 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)
- Meningioma or history of meningioma
- Undiagnosed vaginal bleeding
- Concomitant use with another hormonal contraceptive
- Known or suspected pregnancy
- Lactation
- Hypersensitivity to any of the ingredients in DIANE-35 ED.

DIANE-35 ED is not for use in men.

4.4 Special warnings and precautions for use

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

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

Circulatory Disorders

Epidemiological studies have suggested an association between the use of COCs containing ethinylestradiol and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as MI, stroke, DVT and PE. These events occur rarely in average-risk women.

Risk of venous thromboembolism (VTE)

The use of any combined hormonal contraceptive (CHC) increases the risk of VTE compared with no use. The woman should be advised that her VTE risk is highest in the first ever year of use and that there is some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.

Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

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

Overall the risk of VTE in users of low oestrogen 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.

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 COCs.

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.

An additional increase in VTE risk for CHCs containing ≥ 50 µg ethinylestradiol cannot be excluded.

The increased risk of VTE during the postpartum period must be considered (see 4.2 Dose and method of administration, 4.6 Fertility, pregnancy and lactation).

VTE may be life threatening or may have a fatal outcome (in 1-2% of the cases).

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

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see list below).

DIANE-35 ED is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

When considering risk/benefit, the doctor should take into account that the adequate treatment of a condition may reduce the associated risk of thrombosis.

Risk factors for VTE

- Obesity (body mass index over 30 kg/m²). Risk increases substantially as BMI rises
- Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma
- Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors
- Positive family history (VTE ever in a sibling or parent especially at a relatively early age e.g. before 50)
- Biochemical factors that may be indicative of hereditary or acquired predisposition for VTE include Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency
- Other medical conditions associated with VTE include:
 - Cancer
 - Systemic lupus erythematosus
 - Haemolytic uraemic syndrome
 - Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)
 - Sickle cell disease
- Increasing age, particularly above 35 years
- Smoking

In women at risk of prolonged immobilisation (including major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma), it is advisable to discontinue use of DIANE-35 ED (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if DIANE-35 ED has not been discontinued in advance.

If a hereditary predisposition to VTE is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

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

Symptoms of VTE (DVT and PE)

Women should be informed of the symptoms of VTE and be advised to seek urgent medical attention if VTE symptoms develop and to inform the healthcare professional that she is taking a CHC.

Symptoms of DVT can include:

- unilateral swelling of the leg and/or foot 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 discoloured skin on the leg

Symptoms of PE can include:

- sudden onset of unexplained shortness of breath or rapid breathing
- sudden coughing which may be associated with haemoptysis
- sharp chest pain or sudden severe pain in the chest which may increase with deep breathing
- 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).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of CHCs with an increased risk for ATE (e.g. MI, angina pectoris, stroke or TIA). Arterial thromboembolic events may be fatal.

The risk of arterial thromboembolic complications in CHC users increases in women with risk factors. DIANE-35 is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

Risk factors for ATE

- Increasing age, particularly above 35 years
- Smoking
- Hypertension
- Obesity
- Positive family history (ATE ever in a sibling or parent especially at relatively early age e.g. below 50)
- Biochemical factors that may be indicative of hereditary or acquired predisposition for ATE include: hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies, and lupus anticoagulant)
- Migraine
- Other medical conditions associated with adverse vascular events:
 - Diabetes mellitus
 - Polycystic ovary syndrome
 - Hyperhomocysteinaemia
 - Valvular heart disease
 - Atrial fibrillation
 - Dyslipoproteinaemia
 - Systemic lupus erythematosus

Women should be advised not to smoke if they wish to use a CHC. Women over 35 years who continue to smoke should be strongly advised to use a different method of contraception.

If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

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

The user group of Diane-35 ED is likely to include patients that may have an inherently increased cardiovascular risk.

Symptoms of ATE

Women should be informed of the symptoms of ATE and be advised to seek urgent medical attention if ATE symptoms develop and to inform the healthcare professional that she is taking a CHC.

Symptoms of stroke can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body
- sudden trouble walking, dizziness, loss of balance or coordination
- sudden confusion, slurred speech or aphasia; sudden partial or complete loss of vision; diplopia
- sudden, severe or prolonged headache with no known cause
- loss of consciousness or fainting with or without seizure

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

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
- feeling of being full, having indigestion or choking
- sweating, nausea, vomiting or dizziness
- extreme weakness, anxiety, or shortness of breath
- rapid or irregular heartbeats

Tumours

The most important risk factor for cervical cancer is persistent human papillomavirus (HPV) infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g. cervical screening and sexual behaviour including use of barrier contraceptives.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently taking COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage, occur in women taking COCs.

Malignancies may be life threatening or have a fatal outcome.

Meningioma

The occurrence of meningiomas (single and multiple) has been reported in association with use of cyproterone acetate, especially at high doses of 25 mg and above and for prolonged time. If a patient is diagnosed with meningioma, any cyproterone containing treatment, including DIANE-35 ED, must be stopped, as a precautionary measure.

Other Conditions

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

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the doctor to withdraw the COC and treat the hypertension. Where considered appropriate,

COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

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

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in women with diabetes taking COCs. However, women with diabetes should be carefully observed while taking COCs.

Crohn's disease and ulcerative colitis have been associated with COC use.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

Each beige active tablet contains 31.12 mg of lactose and each white placebo tablet contains 48.25 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose free diet should take this amount into consideration.

Medical Examination/Consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstatement DIANE-35 ED, guided by the contraindications and warnings. This should be repeated periodically during the use of DIANE-35 ED. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of DIANE-35 ED. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests.

Sexually Transmitted Infections including HIV infections and AIDS

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

Reduced Efficacy

The efficacy of DIANE-35 ED may be reduced in the event of missed beige active tablets (see 4.2 Dose and method of administration – Management of Missed Tablets), vomiting or diarrhoea during active tablet-taking (see 4.2 Dose and method of administration – Advice in Case of Gastrointestinal Disturbances) or concomitant medication (see 4.5 Interaction with other medicines and other forms of interaction).

Reduced Cycle Control

With oestrogen/progestogen combinations, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions (see 4.2 Dose 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.

Children and Adolescents

Diane-35 ED is only indicated after menarche.

Use in the Elderly

Diane-35 ED is not indicated after menopause.

Patients with Hepatic Impairment

Diane-35 ED is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal (see CONTRAINDICATIONS).

Patients with Renal Impairment

Diane-35 ED has not been specifically studied in renally impaired patients.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on Diane-35 ED

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 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 prescribed any of these medicines should temporarily use a barrier method in addition to DIANE-35 ED 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 hormone-containing beige coated tablets in the Diane-35 ED pack, the hormone-free white coated tablets should be omitted and the next pack be started.

- **Substances increasing the clearance of Diane-35 ED (diminished efficacy of Diane-35 ED by enzyme-induction) e.g.:**

Phenytoin, barbiturates, primidone, carbamazepine, rifabutin, rifampicin and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John's Wort (*Hypericum perforatum*).

- **Substances with variable effects on the clearance of Diane-35 ED, e.g.:**

When co-administered with COCs, many human immunodeficiency virus (HIV)/ hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentration of oestrogen or progestogen. These changes may be clinically relevant in some cases.

- **Substances decreasing the clearance of COCs (enzyme inhibitors)**

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the oestrogen or the progestogen 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 35 µg ethinylestradiol.

Influence of DIANE-35 ED on other Medication

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Breast-feeding

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

The most commonly reported adverse reactions with Diane-35 ED are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. They occur in $\geq 1\%$ of users.

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

System Organ Class	Common ($\geq 1/100$ to $<1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ 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	Headache	Migraine	

System Organ Class	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to <1/1,000)
disorders			
Psychiatric disorders	Depressed mood, Altered mood	Decreased libido	Increased libido
Reproductive system and breast disorders	Breast pain, Breast tenderness	Breast hypertrophy	Vaginal discharge, Breast discharge
Skin and subcutaneous tissue disorders		Rash, Urticaria	Erythema nodosum, Erythema multiforme
Vascular Disorders			Thromboembolism

Laboratory Tests

The use of preparations like DIANE-35 ED may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

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 beige active tablets are: nausea, vomiting and withdrawal bleeding. Withdrawal bleeding may even occur in girls before their menarche, if they have accidentally taken Diane-35 ED.

There are no antidotes and further treatment should be symptomatic.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The pilosebaceous unit comprises the sebaceous gland and the hair follicle and is an androgen-sensitive skin component. Acne, seborrhoea, hirsutism and androgenic alopecia are clinical conditions which result from aberrations of this target organ. The clinical conditions may be caused by either an increased sensitivity to or by higher

plasma levels of androgen. Both the substances contained in DIANE-35 ED beneficially influence the hyperandrogenic state. Cyproterone acetate is a competitive antagonist on the androgen receptor, has inhibitory effects on the androgen-synthesis in target cells and produces a decrease on the androgen blood concentration through an anti-gonadotropic effect. This anti-gonadotropic effect is amplified by ethinylestradiol which also up-regulates the synthesis of Sex-Hormone-Binding-Globulin (SHBG) in plasma. By this mechanism, it reduces free, biologically available androgen in the circulation.

Post Authorisation Safety Studies (PASS) have shown that the frequency of VTE diagnosis ranges from 7-10 per 10,000 woman-years in low-oestrogen-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 from 20 to 30 per 10,000 pregnant women or post-partum. Treatment with DIANE-35 ED leads – usually after 3 to 4 months of therapy – to the healing of existing acne efflorescences. The excessive greasiness of the hair and skin generally disappears earlier. The loss of hair which frequently accompanies seborrhoea likewise diminishes. In women experiencing mild forms of hirsutism and in particular, slightly increased facial hair, results do not, however become apparent until after several months of use.

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

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

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 ingestion of a single tablet. Bioavailability is approximately 88 %.

Distribution

Cyproterone acetate is almost exclusively bound to serum albumin. Only 3.5 – 4.0 % of the total serum drug concentrations are present as free steroid. The ethinylestradiol-induced increase in sex hormone binding globulin (SHBG) does not influence the serum protein binding of cyproterone acetate. The apparent volume of distribution of cyproterone acetate is approximately 986 ± 437 L.

Biotransformation

Cyproterone acetate is almost completely metabolised. The main metabolite in plasma was identified as 15beta-OH-CPA which is formed via the cytochrome P450 enzyme CYP3A4. The clearance rate from serum is about 3.6 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 approximately 1.8 days.

Steady-state conditions

Cyproterone acetate pharmacokinetics are not influenced by SHBG levels. Following daily ingestion drug serum levels increase about 2.5-fold reaching steady-state conditions during the second half of a treatment cycle.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of approximately 71 pg/mL are reached at 1.6 hours. During absorption and first-liver passage, ethinylestradiol is metabolised extensively, resulting in a mean oral bioavailability of approximately 45 % with a large interindividual variation of approximately 20-65 %.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98%) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 2.8 – 8.6 L/kg was determined.

Biotransformation

Ethinylestradiol is subject to pre-systemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulphate. The clearance rate was reported to be approximately 2.3-7 mL/min/kg.

Elimination

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

Steady-state conditions

Steady-state conditions are reached during the second half of a treatment cycle when serum drug levels are higher by 60 % as compared to single dose.

5.3 Preclinical Safety Data

Ethinylestradiol

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

Cyproterone acetate

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

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

Embryotoxicity/Teratogenicity

Investigations into embryotoxic or teratogenic effects, using the combination of the two active ingredients, showed no effects indicative of a general teratogenic effect following treatment during organogenesis before development of the external genital organs. Administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs (after approx. day 45 of pregnancy) could lead to signs of feminisation in male foetuses following higher doses. Observation of male newborn children who had been exposed *in utero* to cyproterone acetate did not show any signs of feminisation. However, pregnancy is a contraindication for the use of DIANE-35 ED.

Genotoxicity and Carcinogenicity

Recognised first-line tests of genotoxicity gave negative results when conducted with cyproterone acetate. However, further tests showed that cyproterone acetate was capable of producing adducts with DNA (and an increase in DNA repair activity) in liver cells from rats and monkeys and also in freshly isolated human hepatocytes, whereas the DNA-adduct level in dog liver cells was extremely low.

This DNA-adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. *In vivo* consequences of cyproterone acetate treatment were the increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats and an increase of mutation frequency in transgenic rats carrying a bacterial gene as target for mutations.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone
Magnesium stearate
Sucrose
Macrogol 6000
Calcium carbonate
Purified talc
Glycerol
Titanium dioxide
Iron oxide yellow
Glycol montanate.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

3 calendar-packs containing 28 tablets.

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

6.6 Special precautions for disposal

No special requirements.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Bayer New Zealand Limited
3 Argus Place
Hillcrest
North Shore
Auckland 0627

Free Phone 0800 233 988

9. DATE OF FIRST APPROVAL

31 March 1992

10. DATE OF REVISION OF THE TEXT

08 March 2021

Summary table of changes

Section changed	Summary of new information
4.3 Contraindications	Updates regarding meningioma
4.4 Special warnings and precautions for use	Updates regarding meningioma