ESTELLE®- 35 ED

PRODUCT INFORMATION

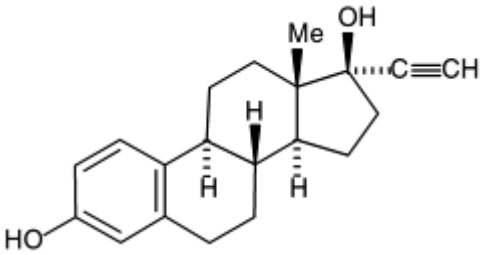
Estelle - 35 ED (Cyproterone acetate / Ethinyloestradiol) tablets

NAME OF THE MEDICINE

Estelle-35 ED is a progestogen oestrogen combination for the treatment of signs of androgenisation in the woman. At the same time, it is a reliable contraceptive for women who suffer primarily from these signs or in whom acne and similar conditions occur or deteriorate under the use of other ovulation inhibitors

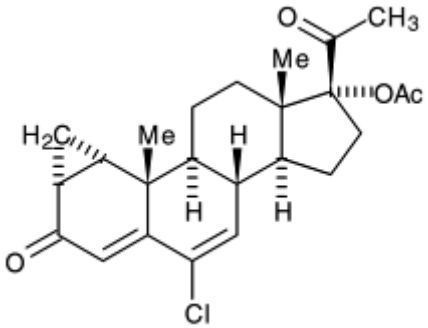
Estelle-35 ED contains the synthetic progestogen, cyproterone acetate and the synthetic oestrogen, ethinyloestradiol.

Ethinyloestradiol:
The chemical name for ethinyloestradiol is 19-nor-17a-pregna-1,3,5,(10)-triene-20-yne-3,17β-diol and has the following chemical structure:



Chemical Formula: $C_{20}H_{24}O_2$ Molecular mass: 296.4 CAS no. 57-63-6

Cyproterone acetate:
The chemical name for cyproterone acetate is 6-chloro-17α hydroxy-1α,2α-methylene-pregna-4,6-diene-3,20-dione actetate and has the following chemical structure:



Chemical Formula: $C_{24}H_{29}ClO_4$ Molecular mass: 416.9 CAS no. 427-51-0

DESCRIPTION

Cyproterone acetate is a white or almost white, crystalline powder, practically insoluble in water, very soluble in methylene chloride, freely soluble in acetone, soluble in methanol, sparingly soluble in ethanol. It melts at about 210°C.

Ethinyloestradiol is a white or slightly yellowish-white, crystalline powder. M.P. 181 - 185°C.

Ethinyloestradiol is practically insoluble in water, freely soluble in ethanol (96%) and ether, sparingly soluble in chloroform. It dissolves in dilute alkaline solutions. It shows polymorphism.

Other ingredients contained in **Estelle-35 ED** tablets are: lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, ethanol, Opdary White Y-IR-7000B, Opadry Buff OY-3690, Eurolake Quinoline Yellow, Opaglos 6000 White, and sucrose (hypromellose, titanium dioxide , macrogol 400, indigo carmine aluminium lake, iron oxide yellow, iron oxide red , iron oxide black, ethanol, shellac, carnauba wax yellow, beeswax white. The placebo tablets contain lactose monohydrate, microcrystalline cellulose and magnesium stearate.

PHARMACOLOGY

Pharmacodynamic Properties

The substance cyproterone acetate contained in **Estelle-35 ED** blocks the effect of endogenously produced and exogenously administered androgens at the target organs by means of competitive inhibition. This results in a gradual regression of signs of androgenisation, irrespective of whether increased androgen values or increased peripheral sensitivity are the cause of the disorder. The decrease in androgen concentration at the target organs has an additional therapeutic effect.

While **Estelle-35 ED** is being taken, the increased sebaceous gland function, which plays an important role in the development of acne and seborrhoea, is reduced. This leads - usually after 3 to 4 months of therapy - to the healing of existing acne efflorescences. The excessive greasiness of the hair and skin generally disappears earlier. The loss of hair which frequently accompanies seborrhoea likewise diminishes. Treatment with **Estelle-35 ED** is indicated in women of childbearing age who exhibit mild forms of hirsutism, and in particular in slightly increased facial hair; results do not, however, become apparent until after several months of use.

Apart from the described anti-androgen effect, cyproterone acetate has also a pronounced progestational action. The combination of ethinyloestradiol and cyproterone acetate prevents a possible pregnancy by the inhibition of ovulation, the inspissation of cervical mucus so as to constitute a barrier to sperm, and the rendering of the endometrium unreceptive to implantation.

As well as protection against pregnancy, combined oral contraceptives (COCs) have several positive properties which, next to the negative properties (see PRECAUTIONS, ADVERSE EFFECTS), can be useful in deciding on the method of birth control. For the majority of users, the cycle is more regular, the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. In addition, with the higher-dosed COCs (> 35 µg ethinyloestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy, endometrial and ovarian cancer. These additional benefits have only been established in case control and cohort studies. Results from randomised controlled trials are not available.

Pharmacokinetics

In a bioequivalence study **Estelle-35 ED** was compared to a tablet containing cyproterone acetate and ethinyloestradiol. Orally both substances are completely absorbed from the **Estelle-35 ED** tablet, ethinyloestradiol being slightly faster. Maximum plasma levels can be expected within 1hour to 4 hours. The mean C_{max} and median T_{max} values were 12.8 ng/mL and 1.51 hours respectively for cyproterone and 406 pg/mL and 1.46 hours respectively for ethinyloestradiol. The course of the post-maximum concentration is characterised by a two-phase decrease with half-lives of 3-4 hours and 2 days for cyproterone acetate and 1-3 hours and approx. 1 day for ethinyloestradiol.

Because the plasma half-life of cyproterone acetate is twice as long as that of other progestogens, a stable substance level that is scarcely influenced by the individual dose is reached with daily administration.

The two steroids are eliminated mainly as metabolites: cyproterone acetate is eliminated by the kidneys (30%) and with the bile (70%) with a half-life of 2 days, and ethinyloestradiol is eliminated by the kidneys (40%) and with the bile (60%) with a half-life of 1 day.

Approximately 0.2% of the maternal progestogen (cyproterone acetate) dose and approx. 0.02% of the oestrogen dose can be passed on to the infant with the maternal milk.

After oral administration cyproterone acetate is completely bioavailable, while ethinyloestradiol is approximately 40-60% bioavailable.

Carbohydrate metabolism: Depending on the nature and amount of their active substances, ovulation inhibitors may lead to an excessive glucose and plasma insulin reaction (reduced glucose tolerance), especially on oral glucose loading. The changes are generally reversible after discontinuation of medication.

Lipometabolism: Studies of serum lipids and lipoproteins conducted by various groups have produced somewhat inconsistent results. Whereas, for example, the majority of workers found normal or even reduced cholesterol levels, others reported an increase. The results on the behaviour of the phospholipids, which generally increased slightly, show greater consistency - as do also the results for the plasma triglyceride values, which all study groups agree are increased. This appears to correlate with the oestrogen content of oral ovulation inhibitors.

Other metabolic functions: A few authors have observed isolated disturbances of folic acid metabolism. The resultant megaloblastic anaemia proved responsive to the administration of folic acid and vitamin B12 even without withdrawal of the oral ovulation inhibitors.

An effect was also observed on tryptophan and vitamin B6 metabolism (increased xanthurenic acid elimination after tryptophan loading). Some authors see an association between this and the occurrence of depressive states.

INDICATIONS

For 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.
Estelle-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.

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 PRECAUTIONS)
  - Current VTE (on anticoagulants) or history of deep venous thrombosis [DVT] or pulmonary embolism [PE].
  - Known hereditary or acquired predisposition for venous thromboembolism, 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 venous thromboembolism due to the presence of multiple risk factors.
- Presence or risk of arterial thromboembolism (ATE) (see PRECAUTIONS)
  - Current ATE or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA]).
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (eg. anticardiolipin-antibodies and lupus anticoagulant).

- History of migraine with focal neurological symptoms.
- A high risk of arterial thromboembolism 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
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- 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)
- Concomitant use with another hormonal contraceptive
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Lactation.
- Hypersensitivity to any of the ingredients in **Estelle-35 ED**.
- A history of otosclerosis with deterioration during pregnancy.
- A history of herpes gestationis.
- Sickle-cell anaemia.
- Abnormal lipid metabolism.

Estelle-35 ED is not for use in men.

Estelle-35 ED is composed of the progestogen cyproterone acetate and the oestrogen ethinyloestradiol 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 **Estelle-35 ED** is predominantly based on combined oral contraceptives (COCs). Therefore, the following warnings related to the use of COCs apply also for **Estelle-35 ED**.

PRECAUTIONS

If any of the conditions/risk factors mentioned below are present, the benefits of the use of **Estelle-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 on whether use of **Estelle-35 ED** should be discontinued.

Circulatory Disorders

Epidemiological studies have suggested an association between the use of combined oral contraceptives (COCs) containing ethinyloestradiol and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. 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.

It is important that women understand that VTE associated with CHC use is rare in average-risk women (see table below). The risk in pregnancy (5-20 per 10,000 women over 9 months) and the risk in the post-partum period (45 -65 per 10,000 women over 12 weeks) is higher than that as associated with CHC use.

Combined hormonal contraceptive (CHC) in the table below refers to oral contraceptives with a low oestrogen dose (< 50 µg ethinyloestradiol). An additional increase in VTE risk for CHCs containing ≥ 50 µg ethinyloestradiol cannot be excluded.

The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with CHCs, and how her current risk factors influence this risk.

Products that contain the progestagens levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Products containing cyproterone such as **Estelle-35 ED** may have up to twice this level of risk.

Risk[1] of developing a blood clot (VTE) in a year

Women not using a combined hormonal contraceptive (CHC) and not pregnant	About 2 out of 10,000 women[1]
Women using a CHC containing levonorgestrel, norethisterone or norgestimate	About 5-7 out of 10,000 women
Women using a CHC containing etonogestrel or norelgestromin	About 6-12 out of 10,000 women
Women using a CHC containing drospirenone, gestodene, desogestrel or cyproterone[2]	About 9-12 out of 10,000 women
Women using a CHC containing chlormadinone, dienogest or nomegestrol	Not yet known[3]

[1] In any individual woman the risk may be far higher, depending on her underlying risk factors (see below).
[2] While cyproterone is indicated for the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism, it is known to have efficacy as a contraceptive. The risk of VTE associated with cyproterone use is considered to be 1.5 to 2 times higher than for CHCs containing levonorgestrel and may be similar to the risk with contraceptives containing gestodene, desogestrel or drospirenone.
[3] Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products. Where the risk for a particular progestogen is uncertain, the risk of the class should be used in determining the risk for the individual patient.

The increased risk of VTE during the postpartum period must be considered. See *Dosage and Administration*, *Use in Pregnancy* and *Use in Lactation*.

VTE may be life-threatening or may have a fatal outcome (in 1-2% of cases). Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral 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).

Estelle-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 (venous thromboembolism 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 **Estelle-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 **Estelle-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 venous thromboembolism.

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)
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 deep vein thrombosis (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 pulmonary embolism (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 arterial thromboembolism (e.g. myocardial infarction, 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. **Estelle-35 ED** 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 (arterial thromboembolism 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 **Estelle-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 a 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 myocardial infarction (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 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.

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

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. A relationship between COC use and clinical hypertension has not been established. 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, and otosclerosis-related hearing loss.

In women with hereditary angio-oedema exogenous oestrogens may induce or exacerbate symptoms of angio-oedema.

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

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics taking low-dose COCs (containing < 50 µg ethinyloestradiol). However, diabetic women should be carefully observed while taking COCs.

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

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

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

Each yellow active tablet contains 41.19 mg of lactose and each white placebo tablet contains 67 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 reinstitution of Estelle-35 ED, guided by the CONTRAINDICATIONS and PRECAUTIONS, and should be repeated periodically. In general, an annual examination is recommended. 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 COC. 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
Estelle-35 ED does not protect against sexually transmitted infections (STIs), including HIV infections (AIDS). The woman should be advised that additional barrier contraceptive measures are needed to prevent transmission of STIs.

Reduced Efficacy
The contraceptive efficacy of Estelle-35 ED may be reduced in the event of missed yellow active tablets, vomiting, or diarrhoea during yellow active tablet taking (see DOSAGE AND ADMINISTRATION) or concomitant medication (see INTERACTIONS WITH OTHER MEDICINES).

Reduced Cycle Control
With all COCs, 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 placebo tablet interval. If the COC has been taken according to the directions, 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.

Use in Pregnancy (Category B3)
Reproduction toxicity studies with the drug combination did not indicate any teratogenic effects. Animal studies nevertheless showed that cyproterone acetate alone (given at high doses) can cause signs of feminisation in male foetuses if given during the phase of differentiation of the foetal male genital organs. The relevance of these findings to man is not known. Isolated cases of inadvertent use of **Estelle-35 ED** during pregnancy have so far given no indications of a corresponding risk in humans. Despite this, the possibility must be considered that the use of **Estelle-35 ED** during the hormone sensitive phase of differentiation of the genital organs in male foetuses (from about the 45th day of pregnancy) might cause signs of feminisation. For this reason, **Estelle-35 ED** is contraindicated during pregnancy.

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

Use in Lactation
The use of **Estelle-35 ED** is contraindicated during lactation as small amounts of cyproterone acetate are excreted in breast milk. Oestrogen containing oral contraceptives may decrease the quantity and quality of breast milk.

Children and adolescents
Estelle-35 ED is only indicated after menarche.

Use in the Elderly
Estelle-35 ED is not indicated after menopause.

Patients with hepatic impairment
Estelle-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
Estelle-35 ED has not been specifically studied in renally impaired patients.

Carcinogenesis / Mutagenicity
Long-term continuous administration of natural and synthetic oestrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver.

In a long-term carcinogenicity study of CPA in rats, an increased incidence of hepatomas was reported at oral dose levels of 50 mg/kg CPA and above. In mouse (and a second rat) carcinogenicity studies, increases in benign proliferative changes (nodular hyperplasia) in liver cells of female mice and male and female rats were reported at oral doses of 2 mg/kg. Because of shortcomings in these studies (inadequate pharmacokinetic data and the need to reassess the liver pathology), the carcinogenic potential of CPA in animals could not be determined.

The clinical relevance of these findings is presently uncertain. Clinical experience and limited epidemiological data available to date do not appear to have supported an increased incidence of hepatic tumours in humans at the recommended clinical dose of 2 mg/day cyproterone acetate. It should also be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumours.

Genotoxicity
There is limited evidence available in the literature suggesting that oestrogens may be weakly genotoxic at high doses. Ethinyloestradiol was negative in studies for DNA-adduct formation in cultured human liver slices and in assays for gene mutations (bacterial or mammalian cells *in vitro)* and gave equivocal results in assays for chromosomal damage (clastogenic effects were not consistently seen and occurred at high doses).

Cyproterone acetate was negative in a standard battery of genotoxicity studies. However, further tests showed that CPA was capable of producing DNA adducts in hepatocytes in rats, dogs and monkeys *in vivo* and also in freshly isolated rat and human liver cells *in vitro* following metabolism by hydroxysteroid sulfotransferases. This DNA adduct formation occurred at exposures that might be expected to occur with the recommended dose regimen for **Estelle-35 ED**.

CPA increased DNA repair activity in rat and human hepatocytes *in vitro.* CPA was clastogenic in a female rat liver micronucleus test. Other *in vivo* consequences of CPA treatment were an 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 a target for mutations. In all of these positives *in vivo* tests, hepatocyte proliferation is likely to have contributed to the results being positive. CPA had mitogenic activity towards rat hepatocytes in vitro, but not human hepatocytes.

Effect on Laboratory tests
The use of preparations like **Estelle-35 ED** 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.

INTERACTIONS WITH OTHER MEDICINES

Drug interactions that result in an increased clearance of sex hormones can lead to breakthrough bleeding and oral contraceptive failure. The following interactions have been reported in the literature.

Effects of other medicines on Estelle-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.

Women prescribed any of these medicines should temporarily use a barrier method in addition to **Estelle-35 ED** 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 yellow active tablets in the **Estelle-35 ED** pack, the white placebo tablets should be omitted and the next pack be started.

• **Substances increasing the clearance of Estelle-35 ED (diminished efficacy of Estelle-35 ED by enzyme-induction)** Phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John's Wort (*Hypericum perforatum*). The mechanism of this interaction appears to be based on the hepatic enzyme inducing properties of these drugs. Maximal enzyme induction is generally not seen for two to three weeks but may then be sustained for at least four weeks after the cessation of drug therapy

• **Substances with variable effects on the clearance of Estelle-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.

• **Antibiotics (interference with enterohepatic circulation):**
Some clinical reports suggest that enterohepatic circulation of oestrogens may decrease when certain antibiotic agents (e.g. penicillins, tetracylines) are given which may reduce ethinyloestradiol concentrations.

Women prescribed antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after completing a course of antibiotics. If the period in which the barrier method is used runs beyond the end of the active tablets in the COC pack, the white placebo tablets should be omitted and the next COC pack started.

Influence of Estelle-35 ED on other medication:

Oestrogen/progestogen preparations like Estelle-35 ED may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

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

ADVERSE EFFECTS

Various adverse reactions have been associated with oral contraceptive use. The most serious reactions associated with the use of oral contraceptives are discussed under PRECAUTIONS.

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 on whether its use should be discontinued.

System Organ Class	Common (≥ 1/100)	Uncommon (≥ 1/1000 and < 1/100)	Rare (< 1/1000)
Gastrointestinal disorders	Nausea, Abdominal pain	Vomiting, Diarrhoea	
Metabolism and nutrition disorders		Fluid retention	
Psychiatric disorders	Depressed mood, Altered mood	Decreased libido	Increased libido
Nervous system disorders	Headache	Migraine	
Skin and subcutaneous tissue disorders		Rash, Urticaria	Erythema nodosum, Erythema multiforme
Eye disorders			Contact lens intolerance
Reproductive system and breast disorders	Breast pain, Breast tenderness	Breast hypertrophy	Vaginal discharge, Breast discharge
Immune system disorders			Hypersensitivity
Investigations	Increase weight		Decreased weight
Vascular Disorders			Thromboembolism

Other adverse reactions:
Eyes disorders: cataract.

DOSAGE AND ADMINISTRATION

Combined oral contraceptives, when taken correctly have a failure rate of approximately 1% per year.

Estelle-35 ED is to be taken regularly in order to achieve therapeutic efficacy and the required contraceptive protection. Previously used hormonal contraception should be discontinued. The dose regimen of **Estelle-35 ED** is similar to the usual regimen of most of the combined oral contraceptives. Thus, the same administration rules must be considered. The irregular intake of **Estelle-35 ED** can lead to intermenstrual bleeding and could deteriorate the therapeutic and contraceptive reliability. Therapy should not be initiated unless pregnancy has been excluded.

Duration of Treatment

Treatment will probably need to be continued for about 6 months and probably much longer to gain an acceptable therapeutic effect, especially if **Estelle-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 **Estelle-35 ED** is stopped.

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

How to take Estelle-35 ED

The first tablet is taken on the first day of a menstrual period, from the red section of the calendar pack marked with the appropriate day of the week. A tablet is then taken daily until the pack is empty. A new pack is commenced on the very next day, again selecting the appropriate tablet from the red section.

A bleeding usually occurs whilst the white inactive tablets are being taken.

The tablet should be swallowed whole, with a little water. The time of day at which the tablet is taken is immaterial, but once a time has been chosen, the patient should keep to it every day; for example, after breakfast or at bed-time.

Instructions for the Patient: **Estelle-35 ED** has been prescribed for you to treat acne, excessive hair or other skin conditions responding to anti-androgen therapy. It is also an effective oral contraceptive if the following advice is followed.

Estelle-35 ED is not for use in men.

How to start Estelle-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). Additional non-hormonal contraceptive methods must be used for the next 14 days.

- **Changing from a combined hormonal contraceptive (combined oral contraceptive/ COC), vaginal ring**

The woman should start with Estelle-35 ED on the day after the last active tablet (the last tablet containing the active substances) of her previous COC.

In case of a vaginal ring has been used the woman should start taking Estelle-35 ED 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 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 in all of these cases should be advised to additionally use an additional 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 next 14 days.

- **After childbirth or a second trimester abortion**

Women should be advised to start 21 to 28 days after delivery or second-trimester abortion.
Additional non-hormonal contraceptive methods are necessary for the next 14 days. If intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

Estelle-35 ED should not be used in breastfeeding women. See PRECAUTIONS (Use in lactation).

Additional Contraceptive Precautions

When additional contraceptive precautions are required the woman should be advised either to abstain from sex, or to use a barrier method of contraception, such as a cap (or diaphragm) plus spermicide, or for her partner to use a condom. Rhythm methods should not be advised as the pill disrupts the cyclical changes associated with the natural menstrual cycle e.g. changes in temperature and cervical mucus.

- If a tablet of **Estelle-35 ED** is forgotten, it must, without fail, be taken within 12 hours of the usual time of day for taking it. Contraceptive reliability depends on no more than 36 hours interval between tablets.
- If this interval is exceeded the forgotten tablet(s) should be taken and regular tablet taking resumed; but an additional non-hormonal method of contraception should be employed for the rest of the cycle.
- If a withdrawal bleeding ("period") fails to occur whilst taking the 7 inactive tablets, tablet taking should be provisionally stopped and medical advice should be sought. A supplementary method of contraception should be used in the meantime.
- Bleeding between periods: Slight spotting or staining is normally of no significance. However, if bleeding persists or is heavy, medical advice should be sought.
- Absorption of the **Estelle-35 ED** may be impaired, with consequent increased risk of pregnancy, by gastrointestinal disease causing diarrhoea and vomiting. If there is doubt that a tablet has been absorbed it should be treated as a missed tablet (2 above).
- Women who use **Estelle-35 ED** are advised not to smoke cigarettes.

- Treatment will probably need to be continued for about 6 months and probably much longer to gain an acceptable therapeutic effect, especially if **Estelle-35 ED** is being used for the treatment of excessive hair. It is possible that the original condition will recur once treatment with **Estelle-35 ED** is stopped.
- Estelle 35-ED should be withdrawn 3 to 4 cycles after the treated condition has completely resolved.

Advice in case of Gastro-intestinal disturbances

In case of severe gastro-intestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3-4 hours after taking an active tablet, the advice concerning management of missed tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she should take the extra tablet(s) needed from another pack.

OVERDOSAGE

There have been no reports of serious deleterious effects from overdose. On the basis of general experience with COCs, symptoms that may occur in case of overdose of active tablets are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

In cases of overdose, it is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdose.

PRESENTATION AND STORAGE CONDITIONS

Estelle-35 ED tablets are available in blister packs consisting of 21 yellow tablets containing cyproterone acetate 2.0 mg and ethinyloestradiol 0.035 mg and 7 white inactive tablets (placebos).

The calendar-pack consists of a foil backed blister platform containing twenty-eight tablets. On the foil reverse side of the platform, the tablets are allocated to days of the week in calendar format. The starting sector is coloured red.

Store below 30°C. Protect from light and moisture.

POISONS SCHEDULE

S4

NAME AND ADDRESS OF SPONSOR

Amneal Pharma Australia Pty Ltd
12 River St,
South Yarra, VIC. 3141

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (The ARTG):
30th May 2003

DATE OF MOST RECENT AMENDMENT:

30 March 2017

REFERENCES:
1. Dinger JC, Heinemann LA, Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. Contracept 2007; 75:344-54.
2. Long-term Active Surveillance Study for Oral contraceptives (LASS), 2nd update report based on study status. May 2009.