

ESTELLE-35 and ESTELLE-35 ED

Cyproterone Acetate/Ethinylloestradiol Tablets

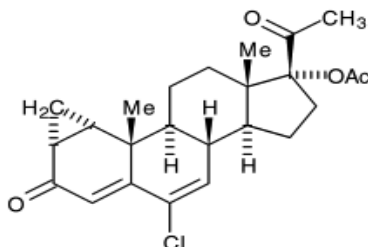
Name of the Medicine

ESTELLE-35 and ESTELLE-35 ED
Cyproterone Acetate/Ethinylloestradiol Tablets

Description

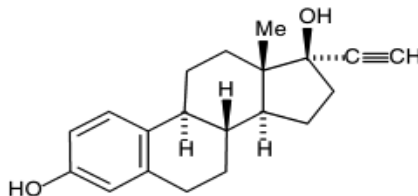
The chemical name of cyproterone acetate is 6-chloro—3,20-dioxo-1 β ,2 β -dihydro-3'H-cyclopropa[1,2]pregna-1,4,6-trien-17-yl acetate. The chemical formula is C₂₄H₂₉ClO₄ and the molecular weight is 416.9.

The structural formula is:



The chemical name of ethinylloestradiol is 19-Nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol, the chemical formula is C₂₀H₂₄O₂ and the molecular weight is 296.4.

The structural formula is:



The yellow active tablets contain as excipients: lactose, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, Opadry White, Opadry Buff, Quinoline yellow, sucrose, Opagloss 6000 white.

The white inactive tablets contain as excipients: lactose, microcrystalline cellulose, and magnesium stearate.

Pharmacology

Mechanism of Action

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 that 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 ESTELLE-35 and ESTELLE-35 ED beneficially influence the hyperandrogenic state. Cyproterone acetate is a competitive antagonist on the androgen receptor, which has inhibitory effects on the androgen-synthesis in target cells and produces a decrease on the androgen blood concentrations through an anti-gonadotropic effect. This anti-gonadotropic effect is amplified by ethinyloestradiol, 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.

Treatment with ESTELLE-35 or ESTELLE-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, also diminishes. In women experiencing mild forms of hirsutism (in particular, slightly increased facial hair) results do not become apparent until after several months of treatment.

The contraceptive effect of ESTELLE-35 and ESTELLE-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 that, 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 combined oral contraceptives (COCs) containing 50 mcg of ethinyloestradiol, there is evidence of a reduced risk of fibrocystic breast tumours, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. This may also apply to lower dosed COCs.

Pharmacokinetics

Cyproterone acetate

Absorption

Following oral administration cyproterone acetate is completely absorbed in a wide dose range. Peak serum concentrations of 15 ng/mL are reached approximately 1.6 hours after ingestion of cyproterone acetate. 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 ethinyloestradiol-induced increase in SHBG does not influence the serum protein binding of cyproterone acetate. The apparent volume of distribution is about 986 ± 437 L.

Metabolism

Cyproterone acetate is almost completely metabolised. The main metabolite in plasma was identified as 15 β -OH-CPA, which is formed via the cytochrome P450 isoenzyme 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 0.8 hours and approximately 2.3 - 3.3 days, respectively. 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 the metabolite excretion is about 1.8 days.

Steady state conditions

The pharmacokinetics of cyproterone acetate 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 the treatment cycle.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of approximately 70 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 sulphate. The clearance rate was reported to be approximately 2.3 – 7 mL/min/kg.

Elimination

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

Steady-state conditions

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

Indications

ESTELLE-35 and ESTELLE-35 ED are not recommended in women solely for contraception.

ESTELLE-35 and ESTELLE-35 ED are indicated for the treatment of androgen-dependent diseases in women, such as acne (where oral antibiotics or local treatment alone has not been successful), especially pronounced forms and those which are accompanied by seborrhoea or by inflammation or formation of nodes (acne papulopustulosa, acne nodulocystica), androgenic alopecia, mild forms of hirsutism.

ESTELLE-35 and ESTELLE-35 ED are also indicated for oral contraception in women requiring treatment for these androgen-dependent diseases; it is not recommended in women solely for contraception. ESTELLE-35 and ESTELLE-35 ED are also indicated for treating the symptoms of polycystic ovary syndrome.

Contraindications

Preparations containing oestrogen/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 use, the product should be stopped immediately.

- Presence or a history of venous or arterial thrombotic/thromboembolic events (eg. deep venous thrombosis, pulmonary embolism, myocardial infarction) or a cerebrovascular accident
- Presence or history of prodromi for a thrombosis (eg. transient ischaemic attack, angina pectoris)
- History of epilepsy
- History of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication
- Pancreatitis or a history of pancreatitis 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 (eg: of the genital organs or the breasts)
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Lactation
- Hypersensitivity to any of the ingredients of ESTELLE-35 or ESTELLE-35 ED

ESTELLE-35 and ESTELLE-35 ED are not for use in men.

Precautions

The clinical and epidemiological experience with oestrogen/progestogen combinations like ESTELLE-35 and 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 and ESTELLE-35 ED.

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

Circulatory Disorders

Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely.

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COC's. The approximate incidence of VTE in users of low oestrogen dose (<50 mcg EE) OC's is up to 4 per 10,000 woman years compared to 0.5 - 3 per 10,000 woman years in non-COC users. However, the incidence of VTE occurring during COC use is substantially less than the incidence associated with pregnancy (i.e. 6 per 10,000 pregnant woman years).

Extremely rarely, thrombosis has been reported to occur in other blood vessels (eg. hepatic, mesenteric, renal or retinal veins and arteries) in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

Symptoms of venous or arterial thrombotic/thromboembolic events or of a cardiovascular accident can include: unilateral leg pain and/or swelling; sudden severe chest pain, regardless of whether it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen.

The risk of thromboembolism (venous and/or arterial) increases with:

- Age
- Smoking (with heavier smoking and increasing age the risk further increases especially in women over 35 years of age)
- A positive family history (i.e. venous or arterial thromboembolism even in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.
- Obesity (body mass index over 30 kg/m²)
- Dyslipoproteinaemia
- Hypertension

- Migraine
- Valvular heart disease
- Atrial fibrillation
- Prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations, it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete mobilisation.

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

The increased risk of thromboembolism in the puerperium must be considered.

Other medical conditions, which have been associated with adverse circulatory events include: diabetes mellitus, polycystic ovary syndrome, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell anaemia.

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

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).

When considering risk/benefit, the doctor should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with COC use.

Tumours

The most important risk factor for cervical cancer is persistent human papilloma virus (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 the confounding effects (eg: cervical screening and sexual behaviour including use of barrier contraceptives).

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR=1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of 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 users tend to be less advanced clinically than the cancers diagnosed in non users.

In rare cases, benign, 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 hepatic 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.

Other precautions

Women with hypertriglyceridemia, or a family history of hypertriglyceridemia, 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.

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 that initially occurred 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 diabetes using COCs. However, diabetic women should be carefully observed while taking COCs.

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

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

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

Medical examination

A complete medical history and physical examination should take place prior to the initiation or reinstatement of ESTELLE-35 or ESTELLE-35 ED, guided by the contraindications and warnings. This should be repeated periodically during the use of ESTELLE-35 or ESTELLE-35 ED.

Periodic medical assessment is also of importance because contraindications (eg. a transient ischaemic attack) or risk factors (eg: a family history of venous or arterial thrombosis) may appear for the first time during the use of ESTELLE-35 or ESTELLE-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.

Women should be advised that ESTELLE-35 and ESTELLE-35 ED do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced Efficacy

The efficacy of ESTELLE-35 or ESTELLE-35 ED may be reduced in the event of missed tablets, vomiting or concomitant medication.

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 an irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, 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 suggested 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 bleeding or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

Use in Pregnancy

The administration of ESTELLE-35 or ESTELLE-35 ED is contraindicated in pregnancy.

If pregnancy occurs during medication with ESTELLE-35 or ESTELLE-35 ED, the preparation is to be withdrawn immediately.

Use in Lactation

The administration of ESTELLE-35 or ESTELLE-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 ethinyloestradiol could be transferred to the newborn via milk.

Effects on Ability to Drive or Operate Machinery

No negative effects have been observed.

Pre-Clinical 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 approximately 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 one of the contraindications for the use of ESTELLE-35 or ESTELLE-35 ED.

Genotoxicity and carcinogenicity

Recognised first-line tests for 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 a target for mutation.

Clinical experience and well-conducted epidemiological trials to date do not support an increased incidence of hepatic tumours in man. Nor did investigations into the tumorigenicity of cyproterone acetate in rodents reveal any indication of specific tumorigenic potential. However, it must be borne in mind that sexual 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 ESTELLE-35 or ESTELLE-35 ED in humans if used in accordance with directions for the given indication and at the recommended dose.

Interactions

Interactions between oestrogen/progestogen combinations like ESTELLE-35 and ESTELLE-35 ED and other drugs may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

Hepatic metabolism

Interactions can occur with drugs that induce microsomal enzymes, which can result in increased clearance of sex hormones. This has been established for phenytoin, barbiturates, primidone, carbamazepine, rifabutin, rifampicin, oxcarbamazepine, topiramate, felbamate, fitonavir, griseofulvin and products containing St John's wort.

Interference with Enterohepatic circulation

Some clinical reports suggest that enterohepatic circulation of oestrogens may decrease when certain antibiotic agents are given, which may reduce the ethinyloestradiol concentrations (eg: penicillins, tetracyclines).

Women on treatment with any of these drugs should temporarily use a barrier method in addition to ESTELLE-35 or ESTELLE-35 ED or choose another method of contraception. With microsomal enzyme-inducing drugs, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days of discontinuation. If the period during which the barrier method is used includes the inactive tablets, they should not be taken and the next pack started without delay.

Oestrogen/progestogen combinations like ESTELLE-35 and ESTELLE-35 ED may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may be affected (eg: cyclosporin).

Laboratory Tests

The use of preparations like ESTELLE-35 or 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 (eg. 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.

Adverse effects

An increased incidence of the following serious conditions has been associated with the use of oral contraceptives - thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis and haemorrhage, hypertension, gall bladder disease, congenital anomalies.

There is an association between oral contraceptive use and mesenteric thrombosis, benign hepatomas, and neuro-ocular lesions e.g. retinal thrombosis and optic neuritis.

The following undesirable reactions are believed to be drug related. Most common are nausea and vomiting, which may decrease with continued use.

Less common are gastrointestinal symptoms (abdominal cramps and bloating); breakthrough bleeding; spotting; changes in menstrual flow; dysmenorrhoea; amenorrhoea during or after treatment; temporary infertility post treatment; oedema; skin pigmentation which may persist; breast changes: (tenderness, enlargement, and secretion), weight increase or decrease; changes in cervical erosion and cervical secretion; possible diminution in lactation when given post-partum; cholestatic jaundice; pruritus; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced carbohydrate tolerance; vulvovaginal candidiasis.

In addition, the following have been reported as adverse reactions:

Premenstrual-like syndrome; intolerance to contact lenses; changes in corneal curvature (steepening); cataracts; changes in libido; chorea; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; drowsiness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; leg cramps; backache; photosensitivity; fatigue; porphyria; impaired renal function and vaginitis.

Dosage and Administration

ESTELLE-35 and ESTELLE-35 ED are 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 and ESTELLE-35 ED is similar to the usual regimen for most combined oral contraceptives. Thus, the same administration rules must be considered.

The irregular intake of ESTELLE-35 or ESTELLE-35 ED can lead to intermenstrual bleeding and could lead to deterioration of the therapeutic and contraceptive reliability.

How to take ESTELLE-35 or ESTELLE-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 hormonal tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after a 7-day tablet free interval or 7-day period of non-hormonal tablets, during which a withdrawal bleeding usually occurs. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

How to start ESTELLE-35

Where there has been no previous hormonal contraceptive use the first tablet of ESTELLE-35 must be taken on the first day of the cycle (first day of bleeding). Starting on day 2 to 5 is allowed, but during the first cycle a barrier method is recommended for the first 7 days of tablet taking.

Changing from another combined oral contraceptive (COC)

The woman should start with ESTELLE-35 preferably on the day after the hormonal tablet of her previous COC, but at the latest on the day following the usual tablet free or non-hormonal tablet interval of her previous COC.

Changing from a progestogen only method (minipill, injection, implant)

The woman may change any day from the minipill (from an implant on the day of its removal, from an injectable when the next injection would be due) but should in all cases be advised to use additional contraception (barrier methods) for the first 7 days of tablet taking.

Following first trimester abortion

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second trimester abortion

Women should be advised to start at day 21 to 28 after delivery or second trimester abortion. When starting later, the woman should be advised to use additional contraception (barrier methods) for the first 7 days of tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of ESTELLE-35 use or the woman has to wait for her first menstrual period.

How to start ESTELLE-35 ED

Where no preceding hormonal contraceptive use has occurred, ESTELLE-35 ED should be started on the first day of bleeding, taking the tablet in the red section marked with the appropriate day of the week. One yellow hormonal tablet is to be taken daily for 21 consecutive days. The white non-hormonal tablets are then taken daily for 7 days. Withdrawal bleeding should usually occur within 2 - 4 days after taking the last small yellow hormonal tablet.

In the first cycle only, an additional form of contraception (except the rhythm and temperature methods) must be used for the first 14 days of tablet taking.

Tablets should be taken at the same time each day if possible.

Changing from another combined oral contraceptive

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

Changing from a progestogen only method (minipill, injection, implant)

The woman may switch any day from the minipill (from an implant on the day of its removal, from an injectable when the next injection would be due), but should, in all of these cases, be advised to use additional contraception (barrier methods) for the first 14 days of tablet taking.

Following first trimester abortion

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second trimester abortion

Women should be advised to start at day 21 - 28 after delivery or second trimester abortion. When starting later, the woman should be advised to use additional contraception (barrier methods) for the first 14 days of tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of ESTELLE-35 ED use or the woman has to wait for her first menstrual period.

Management of missed tablets

Errors in taking the non-hormonal (white) tablets contained in ESTELLE-35 ED can be ignored.

If one or two yellow hormone tablets have been missed at any time:

- She should take the most recent missed tablet as soon as she remembers
- She should continue taking the remaining tablets daily at her usual time
- She does not require additional contraceptive protection
- She does not require emergency contraception

If three or more yellow hormone tablets have been missed at any time:

- She should take the most recent missed tablet as soon as she remembers
- She should continue taking the remaining tablets daily at her usual time
- She should be advised to use condoms or abstain from sex until she has taken tablets for 7 days in a row.

In addition:

If tablets are missed in Week 1 (Days 1-7) (because the tablet free interval has been extended)

- Emergency contraception should be considered if she had unprotected sex in the tablet-free interval or in week 1

If tablets are missed in Week 3 (Days 15 –21) (to avoid extending the tablet-free interval)

- She should finish the tablets in her current pack and start a new pack the next day; thus omitting the tablet free interval.

Extra Contraceptive Precautions

When you need extra contraceptive precautions, either:

- Do not 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.

Advice in case of vomiting

If severe gastrointestinal disturbances occur, 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 tablet(s) needed from another pack.

How to shift periods or how to delay a period

To delay a period a woman should continue with small yellow hormonal tablets from another pack of ESTELLE-35 or ESTELLE-35 ED without a tablet-free interval or the white non-hormonal 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 non-hormonal tablet in ESTELLE-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).

Length of Use

The length of use depends on the severity of the treated condition and the patient's response. In general, treatment should be carried out over several months.

It is recommended to take ESTELLE-35 or ESTELLE-35 ED for at least another 3 to 4 cycles after the signs have subsided. Should there be a recurrence of the treated condition weeks or months after discontinuation of ESTELLE-35 or ESTELLE-35 ED, treatment should be resumed. A longer period of treatment may be recommended for polycystic ovary syndrome.

Overdosage

There have been no reports of serious deleterious effects from overdose.

Symptoms

Symptoms that may occur in this case are nausea, vomiting and, in young girls, slight vaginal bleeding.

Treatment

There are no antidotes and further treatment should be symptomatic.

Presentation and Storage conditions

ESTELLE-35: One calendar pack contains 21 yellowish buff, round, biconvex, active tablets plain on both sides, with a diameter of 5.0 mm.

Each tablet contains 2 mg cyproterone acetate and 35 micrograms (0.035 mg) ethinyloestradiol.

ESTELLE-35 ED: One calendar pack contains 21 yellow active tablets and 7 white inactive tablets. Each active tablet is a yellowish buff, round, biconvex tablet, plain on both sides with a diameter of 5.0mm, containing 2 mg cyproterone acetate and 35 micrograms (0.035 mg) ethinyloestradiol. Each inactive tablet is a white, round, biconvex, tablet, plain on both sides with a diameter of 7.1 mm.

Storage

Shelf life is 3 years. Store below 30 °C.

Pack quantities

ESTELLE-35: Three calendar packs of 21 tablets.

ESTELLE-35 ED: Three calendar packs of 28 tablets; sample pack containing one calendar pack of 28 tablets.

Medicine Classification

Prescription Medicine.

Name and Address of Sponsor

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Date of Preparation

27 October 2011