Estelle™-35 and Estelle™-35 ED

Cyproterone Acetate / Ethinylestradiol Tablets

douglas

PRESENTATION

Estelle™-35: 21 active tablets that are described as yellow buff, round biconvex coated plain tablets, plain on both faces. Tablet diameter is approximately 5.6 mm.
Estelle™-35 ED: 21 active tablets that are described as yellow buff, round biconvex coated plain tablets, plain on both faces. Tablet diameter is approximately 5.6 mm.
7 placebo tablets that are described as white, round, biconvex tablets, plain on both sides with a diameter of approximately 7.1 mm.

USES

Actions

The substance cyproterone acetate contained in **Estelle™-35** and **Estelle™-35 ED** inhibits the influence of the androgens, which are also produced by the female system. It is thus possible to treat diseases caused by either an increased production of androgens or a particular sensitivity to these hormones.
While **Estelle™-35** and **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 efflorescence. 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** and **Estelle™-35 ED** is indicated in women of child-bearing 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 antiandrogen effect, cyproterone acetate also has a pronounced progestational action. The sole administration of cyproterone acetate would thus lead to cycle disturbances, which are avoided by its combination with ethinylestradiol in **Estelle™-35** and **Estelle™-35 ED**. This holds true as long as the preparation is taken cyclically according to the instructions. The contraceptive effect of **Estelle™-35** and **Estelle™-35 ED** is based on various factors; the most important of which are seen as the inhibition of ovulation and changes in 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 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 ethinylestradiol, 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

Following oral administration cyproterone acetate is completely absorbed in a wide dose range. The ingestion of **Estelle™-35** and **Estelle™-35 ED** effects a maximum serum level of 15 ng cyproterone acetate/mL at 1.6 hours. Thereafter, drug serum levels decrease in two disposition phases characterised by half-lives of 0.8 hours and 2.3 days. The total clearance of cyproterone acetate from serum was determined to be 3.6 mL/min/kg. Cyproterone acetate is metabolised by various pathways including hydroxylations and conjugations. The main metabolite in human plasma is the 15-β-hydroxy derivative.
Some of the dose is excreted unchanged in bile fluid. Most of the dose is excreted in the form of metabolites at a urinary to biliary ratio of 3:7. The renal and biliary excretion was determined to proceed with a half-life of 1.9 days. Metabolites from plasma were eliminated at a similar rate (half-life of 1.7 days).
Cyproterone acetate is almost exclusively bound to plasma albumin. About 3.5 - 4.0 % of total drug is present unbound. Because protein binding is nonspecific, changes in sex hormone binding globulin (SHBG) levels do not affect the pharmacokinetics of cyproterone acetate.
Due to the long half-life of the terminal disposition phase from plasma (serum) and the daily intake, cyproterone acetate accumulates during one treatment cycle. Mean maximum drug serum levels increased from 15 ng/mL (day 1) to 21 ng/mL and 24 ng/mL at the end of treatment cycles 1 and 3, respectively. The area under the concentration versus time profile increased 2.2 fold (end of cycle 1) and 2.4 fold (end of cycle 3). Steady-state conditions were reached after about 10 days. During long-term treatment cyproterone acetate accumulates over treatment cycles by a factor of 2.
The absolute bioavailability of cyproterone acetate is almost complete (88 % of dose).

Ethinylestradiol

Orally administered ethinylestradiol is rapidly and completely absorbed. Following ingestion of **Estelle™-35** and **Estelle™-35 ED**, maximum drug serum levels of about 80 pg/mL are reached at 1.7 hours. Thereafter, ethinylestradiol plasma levels decrease in two phases characterised by half-lives of 1-2 hours and about 20 hours. For analytical reasons these parameters can only be calculated for higher doses.
For ethinylestradiol an apparent volume of distribution of about 5 L/kg and a metabolic clearance rate from plasma of about 5 mL/min/kg were determined.
Ethinylestradiol is highly but non-specifically bound to serum albumin. 2 % of drug levels are present in unbound form. During absorption and first liver passage ethinylestradiol is metabolised resulting in a reduced absolute and variable oral bioavailability. Unchanged drug is not excreted. Ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6 with a half-life of about 1 day.
Due to the half-life of the terminal disposition phase from plasma and daily ingestion, steady-state plasma levels are reached after 3-4 days and are higher by 30-40 % as compared to a single dose.
The systemic availability of ethinylestradiol might be influenced in both directions by other drugs. There is, however, no interaction with high doses of vitamin C. Ethinylestradiol induces hepatic synthesis of sex hormone binding globulin (SHBG) and corticoid binding globulin (CBG) during continuous dose. The extent of SHBG induction, however, is dependent on the chemical structure and dose of the co-administered progestin. During treatment with **Estelle™-35** and **Estelle™-35 ED** SHBG concentrations in serum increased from about 100 nmol/L to 300 nmol/L and the serum concentrations of CBG increased from about 50 µg/mL to 95 µg/mL.

Indications

- Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age.
- For the treatment of acne, **Estelle™-35** and **Estelle™-35 ED** should only be used after topical therapy or systemic antibiotic treatments have failed.
- Since **Estelle™-35** and **Estelle™-35 ED** is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives.

DOSAGE AND ADMINISTRATION

Note: Estelle™-35 and Estelle™-35 ED should not be prescribed for the purpose of contraception alone. However, when taken as recommended, Estelle™-35 and Estelle™-35 ED will provide reliable contraception in patients treated for the above clinical conditions. If patient compliance is uncertain and contraception is necessary, then a supplementary non-hormonal contraceptive method should be considered.

Estelle™-35 and **Estelle™-35 ED** are to be taken regularly in order to achieve therapeutic efficacy and the required contraceptive protection. 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** and **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 mini pill (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, start taking **Estelle™-35 ED** on the first day of bleeding, taking the tablet in the red section marked with the appropriate day of the week. Take the small yellow hormonal tablets daily until all 21 of the small yellow hormonal tablets have been taken. Continue by taking the white non-hormonal tablets daily for 7 days. Withdrawal bleeding should usually occur within 2 to 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 mini pill (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 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.

Mismanagement of missed tablets

Errors in taking the non-hormonal tablets contained in **Estelle™-35 ED** can be ignored. If the user is less than 12 hours late in taking any hormonal tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time. If she is more than 12 hours late in taking any hormonal 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 pack. If tablets are missed in the first week of taking hormonal tablets and intercourse took place in the preceding 7 days the possibility of pregnancy should be considered.
The management of missed tablets can be guided by the following two basic rules:
1. Tablet taking must never be discontinued for longer than 7 days.
2. 7 days of uninterrupted tablet taking is required to attain adequate suppression of the hypothalamic-pituitary-ovarian axis.

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 tablets
- You will not be protected from pregnancy until you have taken your daily small yellow hormone tablet for the next 7 days in a row.
- Use another method of contraception (See Extra Contraceptive Precautions) such as condoms or refrain from sexual intercourse for the next 7 days while taking the next 7 small yellow hormone tablets.
- If there are fewer than 7 small yellow hormone tablets left in the pack, finish the small yellow hormone tablets and go straight on to the small yellow hormone tablets of the next pack. This means that you do not leave a gap between the small yellow hormone tablets and you miss out the white non-hormonal tablets if you have 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 vomiting

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*** 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.

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.
- Thrombosis (venous or arterial) present or in history (eg. deep venous thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident).
- Presence or history of prodromi for a thrombosis (eg. transient ischaemic attack, angina pectoris).
- 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.
- 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 malignant conditions of the genital organs or the breasts, if sex steroid-influenced.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Lactation.
- Hypersensitivity to any of the ingredients of **Estelle™-35** or **Estelle™-35 ED**.
- History of migraine with focal neurological symptoms

Estelle™-35 and **Estelle™-35 ED** are not for use in men.
- **Estelle™-35** and **Estelle™-35 ED** is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir (see Warnings and Precautions section and Interactions section).

WARNINGS AND 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.
The risk of VTE is highest during the first year of use. This increased risk is present after initially starting COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly during the first 3 months.
Overall the risk for venous thromboembolism (VTE) in users of low estrogen 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.
VTE may be fatal (in 1-2 % of cases).
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 to 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 (ie. 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 deep venous thrombosis (DVT) can include: unilateral swelling of the leg 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 bring up blood; sharp chest pain which may increase with deep breathing; sense of anxiety; 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).
An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion or myocardial infarction (MI).
Symptoms of a cerebrovascular accident can include: sudden numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding;

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sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoleration of an extremity; acute abdomen.
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; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness; anxiety, or shortness of breath; rapid or irregular heartbeats.
Arterial thromboembolic events may be fatal.
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 (ie. 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/m^2).
- Dyslipoproteinaemia
- Hypertension
- 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, 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 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 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 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 lead 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 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. 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.
In women with hereditary angioedema, exogenous estrogen may induce or exacerbate symptoms of angioedemia.
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 which initially occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of 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 symptoms of chloasma have recently developed or increased substantially in women suffering from hirsutism, the causes (androgen-producing tumours, adrenal enzyme defect) must be clarified by differential diagnosis.
Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 100 mg or more of Cyproterone Acetate. Most reported cases are in men with prostate cancer. Toxicity is dose related and develops, usually several months after treatment has begun. Liver function tests should be performed pre-treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, Cyproterone Acetate should normally be withdrawn, unless the hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case Cyproterone Acetate should be continued only if the perceived benefit outweighs the risk.
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.

ALT elevations
During clinical trials with patients treated for hepatitis C virus infections (HCV) with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with/without ribavirin, transaminase (ALT) elevation higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Patient who are taking ethinylestradiol-containing medicinal products must switch to an alternative method of contraception (e.g. progestin only contraception or non-hormonal methods) prior to initiating ombitasvir/paritaprevir/ritonavir and dasabuvir therapy (see Contraindications section and Interactions section).

Medical examination/consultation
A complete medical history and physical examination should take place prior to the initiation or reinstitution of **Estelle™-35** or **Estelle™-35 ED**, guided by the contraindications and warnings. This should be repeated at least annually during the use of **Estelle™-35** or **Estelle™-35 ED**. Periodic medical assessment is also of importance because contraindications (eg. a transient ischaemic attack, etc) 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 recent laboratory tests.
Women should be advised that preparations like **Estelle™-35** or 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. See Interactions and Dosage and Administration.

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.

PREGNANCY AND LACTATION

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 ethinylestradiol could be transferred to the newborn via milk.

Effects on ability to drive and use machinery
No negative effects have been observed.

PRE-CLINICAL SAFETY DATA

Systemic Toxicity
In animal-experimental systemic tolerance studies following repeated oral administration, no signs of systemic intolerance were observed which might prohibit use in humans at the dose required for the given indications.
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 gravidity) could lead to signs of feminisation in male foetuses following higher doses. Observation of male newborn children who had been exposed in utero to cyproterone acetate did not show any signs of feminisation. However, pregnancy is a contraindication 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. This DNA-adduct formation occurred with exposure that might be expected to occur in the recommended dose regimens for cyproterone acetate. In vivo consequences of cyproterone acetate treatment were the increased incidence of focal, possibly pre neoplastic, liver lesions in which cellular enzymes were altered in female rats 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 would 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.

ADVERSE EFFECTS

Serious undesirable effects of **Estelle™-35** or **Estelle™-35 ED** have been referred to in the contraindications and warnings and precautions sections.
The following undesirable effects have been reported in users of **Estelle™-35** or **Estelle™-35 ED** and the association has been neither confirmed nor refuted:
Nausea, vomiting, abdominal cramps, breakthrough bleeding, breast tenderness, changes in menstrual flow, changes in cervical erosion and cervical secretions, amenorrhoea during and after treatment, anovulation post treatment, allergic rash, photosensitivity, poor tolerance to contact lenses, alopecia, erythema multiforme, erythema nodosum, haemorrhagic eruption, headache, depressive moods, migraine, dizziness, drowsiness, changes in appetite, body weight and libido can occur.

Vascular Disorders
Rare: Thromboembolism

INTERACTIONS

Drug interactions which result in an increased clearance of sex hormones can lead to breakthrough bleeding and oral contraceptive failure. This has been established for hydantoins, barbiturates, primidone, carbamazepine and rifampicin; oxcarbamazepine, topiramate, felbamate and griseofulvin are also suspected. The mechanism of interaction appears to be based on the hepatic enzyme-inducing properties of these drugs. Maximal enzyme induction is generally not seen for 2-3 weeks but may then be sustained for at least 4 weeks after the cessation of drug therapy.
Contraceptive failures have also been reported with antibiotics, such as ampicillins and tetracyclines. The mechanism of this effect has not been elucidated.
Women on short-term treatment with any of the above mentioned classes of drugs or individual drugs should temporarily use a barrier method in addition to **Estelle™-35** or **Estelle™-35 ED**, ie. during the time of concomitant drug administration and for 7 days after their discontinuation. For women on rifampicin, a barrier method should be used in addition to **Estelle™-35** or **Estelle™-35 ED** during the time of rifampicin administration and for 4 weeks after its discontinuation.
If concomitant drug administration runs beyond the end of the tablets in the **Estelle™-35** or **Estelle™-35 ED** pack, the next **Estelle™-35** or **Estelle™-35 ED** pack should be started without the usual tablet free interval.
In women on long-term treatment with hepatic enzyme-inducing drugs, experts have recommended an increase in the contraceptive steroid doses. If a high contraceptive dosage is not desirable or appears to be unsatisfactory or unreliable, eg. in the case of irregular bleeding, another method of contraception should be used.

Medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin
Concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see Contraindications section and Warnings and Precautions section). Therefore, users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. EstelleTM-35 or EstelleTM-35 ED can be restarted 2 weeks following completion of treatment with this combination drug regimen.

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.

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.

PHARMACEUTICAL PRECAUTIONS

Shelf-life is 36 months or 3 years. Store below 30 °C.

MEDICINE CLASSIFICATION

Prescription Medicine

Package Quantities
Estelle™-35: 21's and 21's x 3
Estelle™-35 ED: 28's and 28's x 3

FURTHER INFORMATION

The chemical name of cyproterone acetate is 6-chloro-17-hydroxy-1α,2α-methylenepregna-4,6-diene-3,20-dione acetate, the chemical formula is $C_{24}H_{29}ClO_4$ and the molecular weight is 416.9.
The chemical name of ethinylestradiol is 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17β-diol, the chemical formula is $C_{20}H_{24}O_2$ and the molecular weight is 296.4.
The other ingredients in the yellow active tablets include: lactose, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, Opadry white Y-1R-7000B, Opadry buff OY-3690, Quinoline yellow, sucrose, Opagloss 6000 white.
The ingredients in the white inactive tablets include: lactose, microcrystalline cellulose, magnesium stearate.

MANUFACTURED BY

Douglas Manufacturing Ltd
Corner Te Pai Place and Central Park Drive, Lincoln,
Auckland, New Zealand.

MARKETED BY

Douglas Pharmaceuticals Ltd
PO Box 45 027, Auckland 0651

DISTRIBUTED IN MALAYSIA BY

SCHMIDT BioMedTech Sdn. Bhd.
5th Floor Wisma Tecna, 18A, Lot 318, Jalan 51A/223,
46100 Petaling Jaya, Selangor, Malaysia

DATE OF PREPARATION

April, 2016

309012

DOUGLAS CUSTOMER APPROVAL:
Batch Coding Details Approved: N/A (please tick)
Artwork Text and Design Approved: ☐ (please tick)
SIGN AND DATE: _____
douglas UPON RECEIPT OF THIS ARTWORK SIGNED BY THE CLIENT, DOUGLAS CONSIDERS IT "APPROVED FOR PRINTING".

Description: Estelle-35 TAB MY 309012
Size: 400 x 210 mm
Printed: Black (25% - 100%)
Date: Monday 24 September 2018