ESTELLE™-35ED

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT
Estelle-35ED tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
21 hormone-containing small, yellow coated tablets:
Each coated tablet contains 0.035 mg ethinylestradiol, 2.0 mg cyproterone acetate.
7 large non-active white coated tablets:
Each coated non-active tablet contains lactose, microcrystalline cellulose, magnesium stearate.

3. PHARMACEUTICAL FORM
Coated tablet.

4. CLINICAL PARTICULARS
4.1 Indications
For the treatment of androgen-dependent diseases in women, such as moderate to severe acne, and mild forms of hirsutism.

When used for the treatment of acne, Estelle-35ED should only be used after topical therapy or systemic antibiotic treatments have failed.

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.
Estelle-35ED should not be prescribed for the purpose of contraception alone.

4.2 Dosage and Method of Administration
Method of Administration
Oral use.

Dosage Regimen
How to take Estelle-35ED
Estelle-35ED is to be taken regularly in order to achieve the therapeutic efficacy and the required contraceptive protection. Previously used hormonal contraception should be discontinued. The dose regimen of Estelle-35ED is similar to the usual regimen of most of the combined oral contraceptives. Thus, the same administration rules must be considered. Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year. The irregular intake of Estelle-35ED can lead to intermenstrual bleedings and could deteriorate the therapeutic and contraceptive reliability.

Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. One yellow tablet is to be taken daily for 21 consecutive days, followed by one white tablet for 7 days during which time a withdrawal bleed usually occurs. This usually starts on day 2-3 after the last yellow tablet and may not have finished before the next pack is started.

How to start Estelle-35ED
• *No preceding hormonal contraceptive use (in the past month)*
The first yellow tablet has to be started on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2-5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

• *Changing from a combined hormonal contraceptive (Combined oral contraceptive/COC), vaginal ring or transdermal patch*
The woman should start with Estelle-35ED preferably on the day after the last hormone-containing tablet of her previous COC, but at the latest on the day following the usual tablet-free or hormone-free tablet interval of her COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Estelle-35ED preferably on the day of removal of the last ring or patch of a cycle pack, but at the latest when the next application would have been due.

• *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 should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

• *Following first-trimester abortion*
The woman may start immediately. When doing so, she does not need additional contraceptive measures.

• *Following delivery or second-trimester abortion*
For breastfeeding women see section, "Pregnancy and Lactation".

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 additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of Estelle-35ED use or the woman has to wait for her first menstrual period.

Management of missed tablets
If the user is **less than 12 hours** late in taking any yellow tablet, contraceptive protection is not reduced. Missed doses of white inactive tablets contained in Estelled-35ED can be ignored. If she has missed taking a yellow tablet, the woman should take the tablet as soon as she remembers and should take further yellow tablets at the usual time.

If she is **more than 12 hours** late in taking any yellow tablet, contraceptive protection may be reduced.

The management of missed yellow tablets can be guided by the following two basic rules:
1. Yellow tablet-taking must never be discontinued for longer than 7 days
2. 7 days of uninterrupted yellow tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

• *Week 1*
The user should take the last missed yellow tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more yellow tablets are missed and the closer they are to the regular white inactive tablet interval, the higher the risk of a pregnancy.

• *Week 2*
The user should take the last missed yellow tablet as soon as she remembers, even if this means

taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed yellow tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 yellow tablet, the woman should be advised to use extra precautions for 7 days.

• *Week 3*

The risk of reduced reliability is imminent because of the forthcoming white inactive tablet-taking interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed yellow tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options and to use extra precautions for the next 7 days as well.

1. The user should take the last missed yellow tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next pack must be started as soon as the current pack is finished, i.e., no gap should be left between packs. The user is unlikely to have a withdrawal bleed until the end of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. The woman may also be advised to discontinue tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

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

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 tablet-taking, the advice concerning missed tablets, as given in section, “Management of missed tablets”, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

Length of use

The length of use depends on the severity of the symptoms of androgenization and their response to treatment. In general, treatment should be carried out over several months. Time to relief of symptoms is at least three months. Acne and seborrhea usually respond sooner than hirsutism. The need to continue treatment should be evaluated periodically by the treating physician.

Should there be a recurrence of symptoms, weeks or months after discontinuation of tablet-taking, treatment with Estelle-35ED may be resumed. In case of a restart of Estelle-35ED (following a 4-week or greater pill free interval), the increased risk of VTE should be considered (see section, “Special warnings and precautions for use”).

Additional information on special populations

Children and adolescents

Estelle-35ED is only indicated after menarche.

Geriatric patients

Not applicable. Estelle-35ED is not indicated after menopause.

Patients with hepatic impairment

Estelle-35ED is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal. See also section, “Contraindications”.

Patients with renal impairment

Estelle-35ED has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

4.3 Contraindications

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

- Concomitant use with another hormonal contraceptive (see section ‘Indications’)
- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident.
- Presence or a history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- Presence or history of cerebrovascular accident
- History of migraine with focal neurological symptoms.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see ‘Special Warnings and Precautions for Use’) such as:
  - Diabetes mellitus with vascular symptoms
  - Severe hypertension
  - Severe dyslipoproteinaemia
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as activated protein C (APC) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- Severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Lactation.
- Hypersensitivity to the active substances or to any of the excipients.
- Estelle-35ED is not for use in men.

Jaundice or persistent itching during a previous pregnancy, Dubin Johnson syndrome. Rotor syndrome, sickle cell anaemia existing or treated cancer of the breast or the endometrium, disturbances of lipometabolism, a history of herpes of pregnancy, otosclerosis with deterioration during pregnancy.

4.4 Special warnings and precautions for use

Estelle-35ED consistsof 21 yellow tablets containing the progestogen cyproterone acetate and the estrogen ethinylestradiol, and 7 white inactive tablets, and is administered for 28 days of a monthly cycle. The yellow tablets have a similar composition to that of a combined oral contraceptive (COC).

The clinical and epidemiological experience with estrogen/progestogen combinations like Estelle-35ED is predominantly based on combined oral contraceptives (COC). Therefore, the following warnings related to the use of COC apply also for Estelle-35ED.

Warnings
If any of the conditions/risk factors mentioned below is present, the benefits of the use of Estelle-35ED 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 physician. The physician should then decide on whether use of Estelle-35ED should be discontinued.

Duration of use
Time to relief of symptoms is at least three months. The need to continue treatment should be evaluated periodically by the treating physician (see section 'Dosage and Method of Administration').

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, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents. These events occur rarely.

The excess risk for venous thromboembolism (VTE) is highest during the first year of use. This increased risk is present after initially starting a 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 present during the first 3 months. VTE may be life-threatening or may have a fatal outcome (in 1-2 % of the cases).

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs.

Epidemiological studies have shown that the incidence of VTE is 1.5 to 2 times higher in users of cyproterone and ethinylestradiol combinations than in users of levonorgestrel-containing combined oral contraceptives (COCs) and may be similar to the risk for desogestrel / gestodene / drospirenone-containing COCs.

- The user group of Estelle-35ED is likely to include patients that may have an inherently increased cardiovascular risk such as that associated with polycystic ovarian syndrome.
- Epidemiological studies have also associated the use of hormonal contraceptive with an increased risk for arterial (myocardial infarction, transient ischaemic attack) thromboembolism.

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

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 discolored 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; 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 discoloration 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 life-threatening or may have a fatal outcome.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. Estelle-35ED should not be prescribed in case of a negative risk benefit assessment (see section “Contraindications”).

The risk of venous thromboembolic events increases with:

- increasing age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age. Women over 35 years should be strongly advised not to smoke if they wish to use Estelle-35ED);
- a positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use;
- prolonged immobilization, 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 remobilization. Antithrombotic treatment should be considered if the use of Estelle-35ED has not been discontinued in advance.

The risk of arterial thromboembolic complications or of a cerebrovascular accident increases with:

- increasing age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age. Women over 35 years should be strongly advised not to smoke if they wish to use Estelle-35ED);
- dyslipoproteinemia;
- obesity (body mass index over 30kg/m^2)
- hypertension;
- migraine;
- valvular heart disease;
- atrial fibrillation
- a positive family history (arterial thrombosis ever 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 hormonal contraceptive use.

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 (see section "Pregnancy and Lactation").

The user group of Estelle-35ED is likely to include patients that may have an inherently

increased cardiovascular risk such as that associated with polycystic ovary syndrome.

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

An increase in frequency or severity of migraine during Estelle-35ED use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of Estelle-35ED.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician 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 low-dose COCs (<0.05 mg ethinylestradiol).

Women using Estelle-35ED should be specifically pointed out to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, Estelle-35ED use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy (coumarins).

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 the confounding effects e.g., cervical screening and sexual behavior 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 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 may have a fatal outcome.

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

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension

develops during the use of a COC then it is prudent for the physician 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; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

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

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

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing < 0.05 mg ethinylestradiol). 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.

Medical examination/consultation

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

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

Reduced efficacy

The contraceptive effect of Estelle-35ED may be reduced in the event of e.g. missed tablets (section 'Management of missed tablets', gastro-intestinal disturbances (section 'Advice in case of gastro-intestinal disturbances') during tablet taking or concomitant medication (section 'Interaction with other medicinal products and other forms of interaction').

Reduced cycle control

With estrogen/progestogen combinations, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles. If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes

should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the white tablet-taking interval. If the COC has been taken according to the directions described in section "Dosage and method of administration", it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicaments on Estelle-35ED

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

There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical studies in women demonstrate no evidence of an interaction between COCs and non-enzyme inducing antibiotics. Rifampicin and griseofulvin are two enzyme-inducing antimicrobials that are known to reduce the efficacy of COC.

Women on treatment with any of these drugs should temporarily use a barrier method in addition to Estelle-35ED or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the tablets in the Estelle-35ED pack, the next pack should be started without the usual white tablet-taking interval.

Substances increasing the clearance of Estelle-35ED (diminished efficacy of Estelle-35ED by enzyme-induction), e.g.:
phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort.

Substances with variable effects on the clearance of Estelle-35ED, e.g.: When co-administered with Estelle-35ED, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestogen. These changes may be clinically relevant in some cases.

Effects of estrogen/progestogen combinations on other medicaments
Estrogen/progestogen combinations like Estelle-35ED may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporins) or decrease (e.g. lamotrigine).

Other forms of interactions
Laboratory tests
The use of preparations like Estelle-35ED 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.

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

4.6 Pregnancy and lactation

Pregnancy

Estelle-35ED is not indicated during pregnancy. If pregnancy occurs during treatment with Estelle-35ED, further intake must be stopped (see section "Preclinical safety data").

Lactation

The administration of Estelle-35ED is 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 µg/kg. 0.02% of the daily maternal dose of ethinylestradiol could be transferred to the newborn via milk during established lactation.

4.7 Effects on ability to drive or use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of Estelle-35ED.

4.8 Undesirable effects

Side effects that have been reported in users of COCs but for which the association has been neither confirmed nor refuted are*:

System Organ Class	**Common (≥ 1/100)**	**Uncommon (≥ 1/1000 and <1/100)**	**Rare (< 1/1000)**
Eye disorders			Contact lens intolerance
Gastrointestinal disorders	Nausea Abdominal pain	Vomiting Diarrhea	
Immune system disorders			Hypersensitivity
Investigations	Weight increased		Weight decreased
Metabolism and nutrition disorders		Fluid retention	
Nervous system disorders	Headache	Migraine	
Psychiatric disorders	Depressed mood Mood altered	Libido decreased	Libido increased
Reproductivesystem and breast disorders	Breast pain, Breast tenderness	Breast hypertrophy	Vaginal discharge Breast discharge
Skin and subcutaneous tissue disorders		Rash Urticaria	Erythema nodosum Erythema multiforme
Vascular Disorders			Thromboembolism

*The most appropriate MedDRA term (version 12.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

The following serious adverse events have been reported in women using COCs, which are discussed in section 'Special warnings and precautions for use':

- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Cerebrovascular accidents
- Hypertension
- Hypertriglyceridemia
- Changes in glucose tolerance or effect on peripheral insulin resistance

- Liver tumours (benign and malignant)
- Liver function disturbances
- Chloasma
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss, Crohn's disease, ulcerative colitis, cervical cancer

The frequency of diagnosis of breast cancer is very slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see sections "Contraindications" and "Special warnings and precautions for use"**.**

There is an increased risk of thromboembolism for all women who use Estelle-35ED (see"Special warnings and precautions for use".

4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The pilosebaceous unit – consisting of the sebaceous gland and the hair follicle – is an androgen-sensitive skin component. Acne, seborrhea, and hirsutism are clinical conditions resulting from aberrations of this target organ which may be caused by increased sensitivity or higher plasma levels of androgen. Both substances contained in Estelle-35ED influence beneficially the hyperandrogenic state: Cyproterone acetate is a competitive antagonist on the androgen receptor, has inhibitory effects on the androgen-synthesis in target cells and produces a decrease of the androgen blood concentration through an antigonadotropic effect. This antigonadotropic

effect is amplified by ethinylestradiol which upregulates as well the synthesis of Sexual-Hormone-Binding-Globulin (SHBG) in plasma. It thereby reduces free, biologically available androgen in the circulation.

Treatment with Estelle-35ED 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. In women experiencing mild forms of hirsutism and, in particular, slightly increased facial hair, results do not, however, become apparent until after several months of use.

The contraceptive effect of Estelle-35ED 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.

5.2 Pharmacokinetic properties

Cyproterone acetate

Absorption

Orally administered cyproterone acetate is rapidly and completely absorbed. Peak serum concentrations of 15 ng/ml are reached at about 1.6 hours after single ingestion. Bioavailability is about 88%.

Distribution

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

Metabolism

Cyproterone acetate is almost completely metabolized. The main metabolite in plasma was identified as 15β-OH-CPA which is formed via the cytochrome P450 enzyme CYP3A4. The clearance rate from serum is about 3.6 ml/min/kg.

Elimination

Cyproterone acetate serum levels decrease in two phases which are characterized by half-lives of about 0.8 h and about 2.3-3.3 days Cyproterone acetate is partly excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1:2. The half-life of metabolite excretion is about 1.8 days.

Steady-state conditions

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

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 71 pg/ml are reached at 1.6 hours. During absorption and first-liver passage, ethinylestradiol is metabolized 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 presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are

present as free metabolites and as conjugates with glucuronides and sulfate. The clearance rate was reported to be about 2.3-7 ml/min/kg.

Elimination

Ethinylestradiol serum levels decrease in two disposition phases 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 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 to single dose.

5.3 Preclinical safety data

Ethinylestradiol

The toxicity profile of ethinyl estradiol 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

Systemic toxicity

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

Embryotoxicity/teratogenicity

Investigations into embryotoxicity using the combination of the two active ingredients showed no effects indicative of a 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 led to signs of feminization in male fetuses following higher doses. Observation of male newborn children who had been exposed in utero to cyproterone acetate did not show any signs of feminization. However, pregnancy is a contraindication for the use of Estelle-35ED.

Genotoxicity and carcinogenicity

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

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

Clinical experience and well conducted epidemiological trials to date would not support an increased incidence of hepatic tumours in man. Nor did investigations into the tumourigenicity of cyproterone acetate in rodents reveal any indication of a specific tumourigenic potential.

However, it must be borne in mind that 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-35ED in humans if used in accordance with the directions for the given indication and at the recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Yellow tablets: Lactose, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, Opadry white, Opadrybuff, Opagloss white, Quinoline yellow, Sucrose
White tablets: Lactose, microcrystalline cellulose, magnesium stearate

6.2 Incompatibilities

None.

6.3 Shelf life

36 months

6.4 Storage Condition

Store below 25°C

6.5 Presentation
Blister-pack containing 21 small, yellow, active tablets and 7 large, white, non-active tablets.

Store all drugs properly and keep them out of reach of children.

Manufactured by
Douglas Manufacturing Ltd
Central Park Drive, Lincoln
Auckland
New Zealand

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