

New Zealand Data Sheet

1. PRODUCT NAME

Estelle-35® 2 mg/35 microgram film coated tablet
Estelle-35® ED 2 mg/35 microgram film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each active tablet of Estelle-35 and Estelle-35 ED contains:

Cyproterone acetate	2 mg
Ethinylestradiol	35 micrograms

Excipients with known effect

Lactose monohydrate
Sucrose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Estelle-35

Film coated, yellowish buff, round, biconvex, active tablets that are plain on both sides, with a diameter of 5 mm.

Estelle-35 ED

Active tablets are film coated, yellowish buff, round, biconvex tablets that are plain on both sides, with a diameter of 5 mm.

Placebo tablets are white, round, biconvex tablets that are plain on both sides, with a diameter of 7.1 mm.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Estelle-35/Estelle-35 ED is not recommended in women solely for contraception.

Estelle-35/Estelle-35 ED is 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/Estelle-35 ED is also indicated for oral contraception in women requiring treatment for these androgen-dependent diseases; it is not recommended in women solely for contraception. It should not be used in combination with other hormonal contraceptives.

Estelle-35/Estelle-35 ED is also indicated for treating the symptoms of polycystic ovary syndrome.

4.2. Dose and method of administration

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

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

Length of Use

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

Estelle-35/Estelle-35 ED should be withdrawn 3 to 4 cycles after the treated condition has completely resolved. Repeat course of Estelle-35/Estelle-35 ED may be given if the androgen-dependent condition(s) recur. In case of a restart of Estelle-35/Estelle-35 ED (following a 4 week or greater pill free interval), the increased risk of VTE should be considered, *see Section 4.4.*

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 active 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 placebo tablets, during which a withdrawal bleeding usually occurs. This usually starts on day 2-3 after the last active tablet is taken and may not have finished before the next pack is started.

How to start Estelle-35 or Estelle-35 ED

No preceding hormonal contraceptive use (in the past month)

Estelle-35/Estelle-35 ED should be started on day 1 of the women's natural cycle (i.e., the first day of her menstrual bleeding). The first tablet should be selected from the red starting section of the pack. Additional non-hormonal contraceptive methods must be used for the first 14 days of tablet-taking.

Changing from another Combined Oral Contraceptive, vaginal ring, or transdermal patch

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

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

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

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

Following First-Trimester Abortion

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

Following Delivery or Second-Trimester Abortion

For breast-feeding woman, *see Section 4.4.*

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

Management of missed tablets

Errors in taking the white placebo tablets contained in Estelle-35 ED can be ignored. However they should be discarded to avoid unintentionally prolonging the placebo tablet phase. The

following advice only refers to missed yellow active tablets (rows 1 -3 of the blister of Estelle-35 ED, or all tablets in Estelle-35):

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

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

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

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

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

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

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

Extra Contraceptive Precautions
When you need extra contraceptive precautions, either: <ul style="list-style-type: none">• 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.
The 7 Day Rule
<ul style="list-style-type: none">• Continue taking your pills. You will not be protected from pregnancy until you have taken your daily small yellow active pill for the next 7 days in a row.• Use another method of contraception (extra contraceptive precautions) such as condoms or do not have sexual intercourse for the next 7 days while taking the next 7 small yellow active pills.• If there are fewer than 7 small yellow active pills left in the pack, finish the small active pills and go straight on to the small yellow active pills of the next pack. This means that you miss out the large white placebo pills in the 28-day pack. You may not have a period until the end of the next pack. This is not harmful.

Advice in case Gastrointestinal Disturbances

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

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

How to shift periods or how to delay a period

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

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming tablet-free interval or omit the white placebo 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).

Special populations

Elderly population

Estelle-35/Estelle-35 ED is not indicated after menopause.

Renal impairment

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

Hepatic impairment

Estelle-35/Estelle-35 ED is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal, *see Section 4.3*.

Paediatric population

Estelle-35/Estelle-35 ED is only indicated after menarche.

4.3. Contraindications

Preparations containing oestrogen/progestogen combinations should not be used in the presence of any of the conditions listed below. Should any of 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 (e.g., deep venous thrombosis, pulmonary embolism, myocardial infarction) or a cerebrovascular accident
- Presence or history of prodromi for a thrombosis (e.g., transient ischaemic attack, angina pectoris)
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication, *see Section 4.4.*
- History of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Use with the Hepatitis C combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, *see Section 4.4.*
- 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
- Concomitant use with another hormonal contraceptive
- Known or suspected pregnancy
- Lactation
- History of epilepsy
- Pancreatitis or a history of pancreatitis if associated with severe hypertriglyceridemia
- Hypersensitivity to any of the ingredients of Estelle-35 or Estelle-35 ED, *see Section 6.1.*

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

4.4. Special warnings and precautions for use

Estelle 35 and Estelle-35 ED are composed of the progesterone cyproterone acetate and the estrogen ethinylestradiol and is administered for 21 days of a monthly cycle. It has similar composition to that of a combined oral contraceptive.

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 COCs. The risk for VTE is highest during the first year a woman takes a COC. 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.

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

Overall the risk of VTE in users of low oestrogen dose (< 50 micrograms 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 life threatening, or in 1-2 % of cases may be fatal.

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

Symptoms of venous (includes PE and DVT) or arterial thrombotic/thromboembolic (includes MI, vascular occlusion and cerebrovascular accident) events can include: unilateral leg pain and/or swelling; 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; sudden severe pain in the chest which may increase with deep breathing, 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; rapid or irregular heartbeat; sudden onset of unexplained shortness of breath or rapid breathing; sudden onset of coughing which may bring up blood; sudden, severe prolonged headache with no known cause; sudden partial or complete loss of vision; diplopia; sense of anxiety; dizziness; slurred speech or aphasia; sudden confusion; 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; fullness, indigestion or choking feeling; sweating; nausea; vomiting.

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).

Arterial thromboembolic events may be life threatening or 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-35 and Estelle-35ED should not be prescribed in women with a negative benefit assessment, *see Section 4.3*.

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 (< 50 micrograms of ethinylestradiol) 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 (e.g., cervical screening and sexual behaviour including use of barrier contraceptives).

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

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

Malignancies may be life threatening or have a fatal outcome.

Other conditions

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

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

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus;

haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

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

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

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

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

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

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

Medical examination

A complete medical history and physical examination should be taken 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 (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-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.

Sexually Transmitted Infections including HIV infections and AIDS

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

Hepatitis C

During clinical trials with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin, transient, asymptomatic elevations of alanine transaminase (ALT) greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as combined oral contraceptives, contraceptive patches, or contraceptive vaginal rings.

Estelle-35 or Estelle-35 ED must be discontinued 2 weeks prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin. [Product name] can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

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 Section 4.2 and 4.5*.

Reduced Cycle Control

With oestrogen/progestogen combinations, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles. If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the suggested directions, *see Section 4.2*, 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 medicines and other forms of interaction

Effects of other medicines on Estelle-35/Estelle-35 ED

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.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Women prescribed any of these medicines should temporarily use a barrier method in addition to Estelle-35/Estelle-35 ED or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the hormone-containing yellow coated tablets in the Estelle-35 ED, the hormone-free white coated tablets should be omitted and the next pack be started.

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

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

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

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

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

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

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 35 micrograms ethinylestradiol.

Influence of Estelle-35/Estelle-35 ED on other Medication

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

In clinical studies, administration of a hormonal contraceptive containing ethinylestradiol did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g. midazolam) while plasma concentrations of CYP1A2 substrates can increase weakly (e.g. theophylline) or moderately (e.g. melatonin and tizanidine).

Pharmacodynamic interactions

Co-administration of ethinylestradiol-containing medicinal products with direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these has been shown to be associated with increases in alanine aminotransferase (ALT) levels to greater than 20 times the upper limit of normal in healthy female subjects and HCV infected women, *see Section 4.3*.

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

4.6. Fertility, pregnancy and lactation

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.

Breast-feeding

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 new-born via milk corresponding to a dose of about 1 microgram/kg. During established lactation 0.02 % of the daily maternal dose of ethinylestradiol could be transferred to the new-born via milk.

Fertility

No data available.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

The most serious undesirable effects associated with the use of COCs such as Estelle-35 or Estelle-35 ED have been referred to in the Warnings and Precautions, *see Section 4.4*. These include venous and arterial thromboembolic disorders.

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

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

System Organ Class	Common ($\geq 1/100$ to $<1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $<1/1,000$)
Eye disorders			Contact lens intolerance
Gastrointestinal disorders	Nausea, Abdominal pain	Vomiting, Diarrhoea	
Immune system disorders			Hypersensitivity
Investigations	Increased weight		Decreased weight
Metabolism and nutrition disorders		Fluid retention	
Nervous system disorders	Headache	Migraine	
Psychiatric disorders	Depressed mood, Altered mood	Decreased libido	Increased libido
Reproductive system and breast disorders	Breast pain, Breast tenderness	Breast hypertrophy	Vaginal discharge, Breast discharge
Skin and subcutaneous tissue disorders		Rash, Urticaria	Erythema nodosum, Erythema multiforme
Vascular disorders			Thromboembolism/ thromboembolic events

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 (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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

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

Symptoms

Symptoms that may occur in case of taking an overdose of yellow active tablets are: Nausea, vomiting and withdrawal bleeding. Withdrawal bleeding may even occur in girls before their menarche, if they have accidentally taken Estelle-35/Estelle-35 ED.

Treatment

There are no antidotes and further treatment should be symptomatic.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: GENITO URINARY SYSTEM AND SEX HORMONES- Antiandrogens and estrogens, ATC code: G03HB01

Pharmacodynamic effects

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 ethinylestradiol, which also up-regulates the synthesis of Sex Hormone-Binding Globulin (SHBG) in plasma. By this mechanism, it reduces free, biologically available androgen in the circulation. Post Authorisation Safety Studies (PASS) have shown that the frequency of VTE diagnosis ranges from 7-10 per 10,000 woman-years in low-oestrogen-dose (< 50 micrograms ethinylestradiol) COC users. The most recent data suggest that the frequency of VTE diagnosis is approximately 4 per 10,000 woman-years in non-pregnant non-COC users and ranges from 20 to 30 per 10,000 pregnant women or post-partum. Treatment with 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, likewise diminishes. In women experiencing mild forms of hirsutism (in particular, slightly increased facial hair) results do not, however 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 micrograms 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.

Text

5.2. Pharmacokinetic properties

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 to 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 is about 986 ± 437 L.

Biotransformation

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 to 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

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 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.

Biotransformation

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

Elimination

Ethinylestradiol serum levels decrease in two 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 approximately 1 day.

Steady-state conditions

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

5.3. Preclinical safety data

Ethinylestradiol

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

Cyproterone acetate

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

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

Embryotoxicity/Teratogenicity

Investigations into embryotoxic or teratogenic effects, using the combination of the two active ingredients, showed no effects indicative of a general teratogenic effect following treatment during organogenesis before development of the external genital organs.

Administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs (after approximately day 45 of pregnancy) could lead to signs of feminisation in male foetuses following higher doses. Observation of male new-born 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, 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 mutations.

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 the directions for the given indication and at the recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Estelle-35 film coated tablet contains the following excipients:

Croscarmellose sodium; Opaglos white; Lactose monohydrate; Magnesium stearate; Microcrystalline cellulose; Opadry buff; Opadry white; Povidone; Purified water; Quinoline yellow; Sucrose.

Estelle-35 ED film coated tablet contains the following excipients:

Active tablet: Croscarmellose sodium; Lactose monohydrate; Magnesium stearate; Microcrystalline cellulose; Opadry buff; Opadry white; Opaglos white; Povidone; Purified water; Quinoline yellow; Sucrose.

Placebo, white, tablet: Lactose monohydrate; Magnesium stearate; Microcrystalline cellulose.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months from date of manufacture

6.4. Special precautions for storage

Store at or below 30°C

6.5. Nature and contents of container

Estelle-35 film coated tablet:

Blisters of aluminium foil and PVC/PVDC film.
Pack size: 3 x 21 film-coated tablets.

Estelle-35 ED film coated tablet:

Blisters of aluminium foil and PVC/PVDC film.
Pack size: 1 x 28 and 3 x 28 film-coated tablets

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Douglas Pharmaceuticals Ltd
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Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

12 July 2001

10. DATE OF REVISION OF THE TEXT

23 February 2018

Summary table of changes

Section Changed	Summary of new information
All	Revised to reflect SPC format
4.2	<i>Length of use</i> Section updated <i>How to start Estelle-35 and Estelle-35 ED</i> Section merged <i>Management of missed tablets</i> added 12-hours rule and 7 Day Rule text <i>Special population</i> Sections added
4.3	<i>Use with the Hepatitis C combination drug</i> added as per Medsafe Letter
4.4	<i>Circulatory Disorders and Other Conditions</i> Sections updated in line with Innovator's information <i>Hepatitis C</i> added as per Medsafe Letter
4.5, 4.7, 4.9, 5.1	Updated in line with the Innovator's information