Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Estelle 20 micrograms/75 micrograms Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 micrograms ethinylestradiol and 75 micrograms gestodene.

Excipients:
contains 38 mg lactose monohydrate and 20 mg sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet.

White, round, biconvex sugar coated tablets, both sides are without imprinting.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oral contraception.

4.2 Posology and method of administration

How to take Estelle:
The tablets should be taken in the order indicated on the package, every day at approximately the same time. One tablet per day should be taken for 21 days. Each subsequent pack should be started after a 7-day tablet-free interval during which time a withdrawal bleeding will occur. This bleeding usually starts on the 2nd or 3rd day after taking the last tablet, and may not stop until the next pack is started.

How to start taking Estelle:
If no preceding hormonal contraceptive use in the past month:
Taking of the tablets should begin on the first day of the woman's natural cycle (i.e. on the first day of the woman's menstrual bleeding). One may begin taking the pills on day 2 – 5, but in these cases, it is recommended that a barrier method also be used for the first 7 days on which pills are taken during the first cycle.

When replacing another contraceptive pill of the combination type:
The woman should start taking Estelle on the next day after taking the last active tablet in her previous package of contraceptive pills – but no later than the day after the usual tablet-free or placebo-tablet period of her previous contraceptive pill.
When changing from progestogen-only preparations (progestogen-only pills, injection, implant, or from a progestogen-releasing intrauterine system (IUS)):
The woman may change from progestogen-only pills (POPs) on any day. The first tablet should be taken on the day after any tablet of the POP package. When changing from an implant or the IUS, Estelle should be started on the day the implant is removed. When changing from injections, Estelle should be started when the next injection is due to be given. In all these cases, the woman is advised to also use a barrier method for the first 7 days of taking the pills.

After an abortion in the first trimester:
The woman may start taking the pills immediately. If she does so, no further contraceptive steps need be taken.

After delivery or abortion in the second trimester:
For breastfeeding women – see section 4.6.
The woman should be advised to begin taking the tablets on day 21 – 28 after delivery in non-lactating women or after abortion in the second trimester. If she starts later, she should be advised to also use a barrier method during the first 7 days of taking the pills. If she has already had intercourse, the possibility of pregnancy should be excluded before she begins taking the pills, or she should wait for her first menstruation.

Missed tablets:
Missing a tablet for less than 12 hours does not diminish the contraceptive protection. The woman should take the tablet as soon as she remembers, and continue taking the rest of the tablets as usual.

Missing a tablet for more than 12 hours can diminish the contraceptive protection. The two following rules may be helpful in dealing with missed tablets.

1. Taking of the tablets should never be discontinued for longer than 7 days.
2. It takes 7 days of uninterrupted ingestion of the tablets to achieve sufficient suppression of the hypothalamus-pituitary-ovarian axis.

Thus, the following advice can be given in daily practice:

Week 1:
The user should take the last missed tablet as soon as she remembers, even if this means that she needs to take 2 tablets at the same time. From then on, she should continue to take the tablets at the usual time. At the same time, she should use a barrier method, i.e. a condom, for the next 7 days. If she had intercourse during the past 7 days, she should consider the possibility that she might be pregnant. The more tablets have been missed, and the closer this happened to the monthly tablet-free period, the higher the risk of pregnancy.

Week 2:
The user should take the last missed tablet as soon as she remembers, even if this means that she needs to take 2 tablets at the same time. From then on, she should continue to take the tablets at the usual time. If the tablets have been taken correctly for the 7 days prior to the missed tablet, it is not necessary to take any additional contraceptive precautions. If this is not the case, however, or if more than 1 tablet has been missed, the woman should use a barrier method**,** i.e. a condom for the next 7 days.

Week 3:
The risk of reduced protection is imminent because of the approaching tablet-free period. The reduced contraceptive protection can be prevented, however, by adjusting the intake of the tablets. By adhering to either of the following two options, it is, therefore, not necessary to take any additional contraceptive precautions, provided that the tablets have been taken correctly for the 7 days prior to the missed tablet. If this is not the case, the woman should be advised to follow the first of the two choices, and at the same time use a barrier method**,** i.e. a condom for the next 7 days.
1. The user should take the last missed tablet as soon as she remembers even if this means that she needs to take 2 tablets at the same time. From then on, she should continue to take the tablets at the usual time. She begins the next pack immediately after she took the last tablet from the current package; that means no pause between packages. The user will probably not get her menstruation before the end of the second package, but she may experience spotting or withdrawal bleeding on the days when she takes the tablets.
2. The woman can also be advised to stop taking tablets from the current package. In that case, she should have a tablet-free period for up to 7 days, including the days when she missed the tablets, and subsequently continue with the next pack.

If the woman missed the tablets, and subsequently did not get her menstruation in the first normal tablet-free period, she should consider the possibility that she may be pregnant.

What to do in case of vomiting/diarrhoea:
If vomiting occurs within 3 – 4 hours after tablet taking, absorption may not be complete. In this case, the advice concerning missed tablets, described above should be followed. Unless diarrhoea is extremely severe it does not affect the absorption of combined oral contraceptives and therefore use of additional contraception is not necessary. If severe diarrhoea continues for 2 or more days, the procedures for missed pills should be followed. If the woman does not want to change her usual tablet intake, she should take an extra tablet(s) from another blister pack.

How to advance or delay menstruation:
To delay menstruation, the woman should continue with another pack of Estelle without a tablet-free period. Menstruation can be delayed as long as is desired up to the end of the second package, but no longer. While menstruation is being delayed, the woman may experience withdrawal bleeding or spotting. Regular intake of Estelle should be resumed after the normal tablet-free period of 7 days.

To move menstruation to another day of the week than the woman is used to with her current tablet schedule, she can be advised to shorten the next tablet-free period by as many days as she wishes. The shorter the interval, the higher the risk that she will not get her menstruation and will have breakthrough bleeding or spotting while she is taking the next pack (just as when menstruation is being delayed).

4.3 Contraindications

Combined oral contraceptives (COCs) must not be used in the presence of the conditions mentioned below. If such a condition should occur for the first time during use of COCs, the use must be discontinued immediately:
- Venous thromboembolism present or in history (deep venous thrombosis, pulmonary embolism) with or without risk factors (see section 4.4)
- Arterial thromboembolism present or in history (myocardial infarction, cerebrovascular disorder), or prodomal conditions (angina pectoris and transient ischaemic attack) (see section 4.4)
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as antithrombin deficiency, protein C deficiency, protein S deficiency, APC-resistance, antiphospholipid antibodies (anticardiolipin-antibodies, lupus anticoagulant), hyperhomocysteinemia
- Considerable or multiple risk factors for arterial thrombosis (see section 4.4)
- Severe hypertension
- Diabetes, complicated with micro or macro angiopathy
- Severe dyslipoproteinaemia
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breast)
- Presence or history of severe hepatic disorders, as long as liver function tests are not normalised
- Presence or history of benign or malignant liver tumours
- Undiagnosed vaginal bleeding
- Migraine with focal neurological symptoms
- Hypersensitivity to the active substances or to any of the excipients.
- Pancreatitis or a history thereof if associated with severe dyslipoproteinaemia.

4.4 Special warnings and precautions for use

Assessment and examination prior to starting combined oral contraceptives:
Before the start or resumption of treatment with combined oral contraceptives, a complete personal and family medical history must be obtained and pregnancy should be ruled out. Blood pressure should be measured and a physical examination performed if clinically indicated, guided by the contraindications (see section 4.3) and warnings (see "Warnings" in this section). The woman should be instructed to carefully read the user leaflet and adhere to the advice given. The frequency and nature of further periodic checks should be based on established practice guidelines and adapted to the individual woman.

Warnings:
General:
Women should be advised that COCs do not protect against HIV (AIDS) or other sexually transmitted infections (STI).

If any of the risk factors below is present in any individual woman, the benefits of combined oral contraception must be weighed against possible risks in each individual case and discussed with the woman before combined oral contraception is commenced. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors the woman should be advised to contact her physician. The physician must then decide, whether the use of COCs should be discontinued.
Women will need condoms to protec themselves from sexually transmitted diseases.

1. Circulatory disorders:
The use of any COC carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a COC. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1 – 2% of cases.

In several epidemiological studies it has been found that women using combined oral contraceptives with ethinylestradiol, mostly with a dose of 30 mg, and a progestin such as gestodene have an increased risk of VTE compared with those who are using combined oral contraceptives containing less than 50µg ethinylestradiol and the progestin levonorgestrel.

For combined oral contraceptives containing 30µg of ethinylestradiol combined with desogestrel or gestodene compared with those containing less than 50µg of ethinylestradiol and levonorgestrel, the overall relative risk of VTE has been estimated to range between 1.5 and 2.0. The incidence of VTE for levonorgestrel containing combined oral contraceptives with less than 50µg of ethinylestradiol is approximately 20 cases per 100,000 women-years of use. For Estelle the incidence is approximately 30 – 40 cases per 100,000 women-years of use, i.e. additional 10 – 20 cases per 100,000 women-years of use. The impact of the relative risk on the number of additional cases would be the greatest in women during the first year they ever use a combined oral contraceptive when the risk for VTE with all combined oral contraceptives is highest.

Thrombosis in other blood vessels has very rarely been reported, i.e. hepatic, mesenteric, renal or retinal veins and arteries, in users of oral contraceptives. There is no consensus, whether the occurrence of these cases is related to use of COCs.

The risk for development of venous thromboembolism increases with:
- Increasing age.
- A positive family history (e.g. venous thromboembolism in siblings or parents at a relatively young age). In the case of suspected hereditary predisposition, the woman should be referred to a specialist before she decides to use oral contraception.
- Obesity (body mass index above 30 kg/m²).
- Prolonged immobilisation, major surgery, surgery on the legs or major trauma. In such cases, it is recommended that treatment with oral contraceptives be discontinued (in the case of elective surgery at least 4 weeks prior to the operation) and should not be resumed until 2 weeks after complete remobilisation.
- There is no consensus concerning the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

The use of COCs in general has been associated with an increased risk of acute myocardial infarction (AMI) or stroke, a risk that is strongly influenced by the presence of other risk factors (e.g. smoking, high blood pressure, and age) (see also below). These events occur rarely.
- The risk of arterial 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);
- dyslipoproteinaemia;
- obesity (body mass index over 30 kg/m^2);
- hypertension;

- valvular heart disease;
- atrial fibrillation;
- a positive family history (i.e. 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

Symptoms of venous or arterial thrombosis can include:
- unilateral leg pain and/ or swelling;
- sudden severe pain in the chest, whether or not it radiates to the left arm;
- sudden breathlessness;
- sudden onset of coughing;
- any unusual, severe, prolonged headache;
- sudden partial or complete loss of vision;
- diplopia;
- slurred speech or aphasia;
- vertigo;
- collapse with or without focal seizure;
- weakness or very marked numbness suddenly affecting one side or one part of the body;
- motor disturbances;
- 'acute' abdomen.

The increased risk of venous thromboembolism during the puerperal period should be taken into consideration.

Other medical conditions which have been related to circulatory disorders include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or colitis ulcerosa) and sickle cell anaemia.

An increase in the frequency or severity of migraine (which may be prodromal for a cerebrovascular condition) during use of oral contraceptives must lead to consideration of immediate discontinuation of oral contraceptives.

Biochemical factors indicating hereditary or acquired predisposition for venous or arterial thrombosis, include activated protein C (APC) resistance, factor V Leiden mutation, hyperhomocysteinaemia, 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 COC use.

2. Tumours:
Cervical cancer:
In some epidemiological studies an increased risk of cervical cancer has been reported in long term users of COCs, but it is still not clear to which extent this finding may be influenced by impacts of sexual behaviour and other factors, such as human papilloma virus (HPV).

Breast cancer:
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 below 40 years of age, the excess number of breast cancer diagnoses in current and recent users of COC 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 cancer diagnosed in never users.

Liver tumours:
Benign and malignant liver tumours have been reported in users of COCs. These tumours have, in isolated cases, lead to life threatening, intra-abdominal haemorrhage. A liver tumour must be taken into consideration as a differential diagnosis when severe pain occurs in the upper abdomen, if there is hepatomegaly, or if there are signs of intra-abdominal haemorrhage in women taking COCs.

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

In the case of acute or chronic impairment of liver function, the use of Estelle should be stopped until liver function tests have returned to normal. Steroid hormones may be poorly metabolised in patients with impaired liver function.

Even though slight increases in blood pressure have been reported in many women taking COCs, clinically important increases in blood pressure are rare. If persistent clinical hypertension develops during COC use, intake should be discontinued and the hypertension treated. Use of COCs may be resumed, if appropriate, when normotensive values are reached with antihypertensive therapy.

It has been reported that the following conditions may occur, or worsen both during pregnancy and during use of COCs, but the evidence of a relationship is inconclusive: jaundice and/or pruritus in connection with cholestasis; development of gallstones; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; loss of hearing due to otosclerosis.

COCs may have an influence on the peripheral insulin resistance and glucose tolerance. Therefore, diabetics should be closely monitored during COC use.

Estelle contains lactose and sucrose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption or with rare hereditary problems of fructose intolerance should not take this medicinal product.

Worsening of endogenous depression, of epilepsy (see section 4.5 interactions), of Crohn's disease and of ulcerative colitis has been reported during COC use.

Chloasma may occur, in particular in women with a medical history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to sunlight or ultraviolet radiation while taking COCs.

Herbal preparations containing St John's wort (Hypericum perforatum) should not be used while taking Estelle due to the risk of decreased plasma concentrations and reduced clinical effects of Estelle (see section 4.5).

Reduced efficacy:
The efficacy of oral contraceptives may be reduced in the case of missed tablets, severe diarrhoea or vomiting (see section 4.2) or concomitant use of other medicinal product (see section 4.5).

Reduced cycle control:
With all combined oral contraceptives, irregular bleeding (spotting or break through bleeding) may occur, especially during the first months. Hence, the evaluation of any irregular bleeding should be considered after a period of adaptation of approximately 3 cycles.

If bleeding irregularities persist COCs with a higher hormonal content may need to be considered. If bleeding irregularities occur after previously regular cycles, then non-hormonal causes should be considered, and adequate diagnostic measures are indicated to exclude malignancy or pregnancy.

Occasionally withdrawal bleeding during the tablet-free interval may not occur at all. If the tablets have been taken according to the instructions described in section 4.2, it is unlikely that the woman is pregnant. However, if the tablets have not been taken according to the instructions, before the first absent withdrawal bleeding, or if two withdrawal bleedings are overdue, pregnancy should be excluded before COC use is continued.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interaction resulting in elevated clearance of sex hormones may cause breakthrough bleeding and contraceptive failure. This has been established with hydantoins, barbiturates, primidone, carbamazepine and rifampicin; oxcarbazepine, topiramate, griseofulvin, felbamate and ritonavir are also suspected. The mechanism of this interaction seems to rest upon the liver enzyme-inducing properties of these medicinal products. Maximal enzyme induction is generally not visible before 2 – 3 weeks after the start of the treatment, but it may persist for at least 4 weeks after the end of treatment.

Contraceptive failure has also been reported with antibiotics, such as ampicillin and tetracyclins. The mechanism of this action has not been elucidated.

Women undergoing short-term treatment with any of the above mentioned groups, or individual medicinal products, should temporarily use a barrier method along with the contraceptive pills; that means during the time when both this medicinal product and the contraceptive pills are taken, as well as 7 days after the medicinal product is discontinued. Women treated with rifampicin should use a barrier method along with the contraceptive pills during the time when they are treated with rifampicin as well as for 28 days after they stop taking rifampicin. If the intake of another concomitant medicinal product stretches beyond the number of tablets in the contraceptive pill pack, the woman should start the next pack without observing the normal tablet-free period.

For long-term users of medicinal products that induce liver enzymes, use of other contraceptive measures should be advised.

Patients being treated with Estelle should not simultaneously use products/alternative medicinal products containing *Hypericum perforatum* (St. John's wort) as this can lead to loss of contraceptive effect. Withdrawal bleeding and undesirable pregnancy have been reported.

Hypericum perforatum (St. John's wort) increases, by enzyme induction, the amount of enzymes that metabolise medicinal products. The effect of the enzyme induction may last for at least 1-2 weeks after the end of treatment with *Hypericum.*
COC effects on other drugs: oral contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (lamotrigine).

Laboratory tests:
The use of contraceptive steroids can influence the results of certain laboratory tests, including the biochemical parameters of liver, thyroid, adrenal, and kidney function; plasma levels of (transport) proteins, such as corticosteroid-binding globulin and lipid/lipoprotein fractions; the parameters of carbohydrate metabolism, and the parameter of coagulation and fibrinolysis. The changes usually remain within the normal test ranges.

4.6 Fertility, pregnancy and lactation

Estelle is not indicated during pregnancy. If pregnancy occurs during medication with Estelle, the preparation should be withdrawn immediately.

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during pregnancy.

Contraceptive steroids can influence breastfeeding, as they can lower the amount and change the composition of breast milk. Small amounts of contraceptive steroids and/or their metabolites can be excreted in the milk. The use of contraceptive steroids should, therefore, generally not be advised to a breastfeeding mother before her child is completely weaned.

4.7 Effects on ability to drive and use machines

Estelle has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported ADRs (> 1/10) are irregular bleeding, nausea, weight increase, breast tenderness and headache. They occur usually at the beginning of therapy and are transient.

Organ system class	**Common (≥1/100 to < 1/10)**	**Uncommon (≥1/1,000 to < 1/100)**	**Rare (≥1/10,000 to < 1,000)**	**Very rare (≤1/10,000)**
Nervous system disorders	Headache Nervousness			Chorea
Eye disorders	Ocular irritation when wearing contact lenses Visual disturbances			
Ear and labyrinth disorders			Otosclerosis	
Gastrointestinal disorders	Nausea abdominal pain	Vomiting	Cholelithiasis	Pancreatitis
Skin and Subcutaneous tissue disorders	Acne	Rash	Chloasma Etythema nodosum	Erythema multiforme
Metabolism and nutrition disorders		Hyperlipidaemia		
Vascular disorders	Migraine	Hypertension	Venous thromboembolism Arterial thromboembolic disorders	
General disorders and administration site conditions	Weight increase Fluid retention			

Immune system disorders			Lupus erythematosus Hypersensitivity reactions.	
Reproduction system and breast disorders	Irregular bleeding Amenorrhoea Hypomenorrhoea Breast tenderness Vaginitis		Changes in vaginal secretion	
Psychiatric disorders	Changes in libido Depression Irritability			

The following serious adverse events have been reported in women using COCs, see sections 4.3 and 4.4.

- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism
- Arterial thromboembolic disorders
- Liver tumours
- Skin and subcutaneous disorders: chloasma

The frequency of diagnosis of breast cancer is very slightly increased among COC-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 4.3 and 4.4.

4.9 Overdose

No serious harmful effects have been reported with overdoses. Symptoms that can arise in connection with an overdose are: nausea, vomiting, and vaginal bleeding. There is no antidote, and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: hormonal contraceptives for systemic use
ATC code: G03 AA10

The contraceptive effect of contraceptive pills rests on the interaction of various factors, the most important of which are inhibition of ovulation and changes in the endometrium. Along with protecting against pregnancy, COCs have several positive properties which, next to the negative properties (see 4.8 Warnings, Undesirable effects), can be useful in deciding on the method of birth control. The menstrual cycle is more regular and the menstruation is often less painful, and bleeding is ligther. The latter may result in a decrease in the occurrence of iron deficiency.

5.2 Pharmacokinetic properties

Gestodene:
Absorption:
Gestodene, when taken orally, is absorbed quickly and completely. Following a single dose the maximum serum concentration of 4 ng/ml is reached in approximately one hour. Bioavailability is approximately 99%.

Distribution:
Gestodene is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1 – 2% of the total amount of gestodene in serum is found as free steroid, while 50 – 70% is specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the distribution of serum proteins, which causes an increase of the SHBG-bound fraction, and a decrease of the albumin-bound fraction. The apparent distribution volume of gestodene is 0.7 l/kg.

Metabolism:
Gestodene is metabolised completely via the known pathways of steroid metabolism. The metabolic clearance rate from serum is 0.8 ml/min/kg. No interaction occurs when gestodene is taken together with ethinylestradiol.

Elimination:
Serum level of gestodene is reduced at 2 rates. The last rate is characterised by a half-life of 12 – 15 hours.
Gestodene is not excreted unchanged. Its metabolites are excreted in urine and in bile at a ratio of 6:4. The half-life of metabolite excretion is approximately 1 day.

Steady-state:
Pharmacokinetics of gestodene is influenced by the levels of SHBG in serum, which increase to triple values with ethinylestradiol. Upon daily intake, the level of gestodene in serum increases till approximately four times the single dose value, and reaches steady-state within the second half of the treatment cycle.

Ethinylestradiol:
Absorption:
Ethinylestradiol, taken orally, is absorbed quickly and completely. Maximal serum concentration of about 80 pg/ml is reached within 1 – 2 hours. Complete bioavailability, resulting from pre-systemic conjugation and first-pass metabolism, is approximately 60%.

Distribution:
During lactation, 0.02% of the daily maternal dose passes into breast milk.
Ethinylestradiol is predominantly bound non-specifically to albumin (approx. 98.5), and causes increase in serum concentration of SHBG. The apparent distribution volume is found to be approximately 5 l/kg.

Metabolism:
Ethinylestradiol undergoes pre-systemic conjugation both in the mucosa of the small intestine, and in the liver.
Ethinylestradiol is primarily metabolised by aromatic hydroxylation, but many different hydroxylated and methylated metabolites are formed, and found as free metabolites and as glucuronide and sulphate conjugates. The metabolic clearance rate is approximately 5 ml/min/kg.

Elimination:
Serum level of ethinylestradiol is reduced at 2 rates, the last one with a half-life of 24 hours. Unchanged ethinylestradiol is not excreted, but its metabolites are excreted in urine and in bile at a ratio of 4:6. The half-life of metabolite excretion is approximately 1 day.

Steady-state:
Steady-state occurs after 3 – 4 days, and the serum levels of ethinylestradiol are 30 – 40% higher than at single dose.

5.3 Preclinical safety data

Ethinylestradiol and gestodene are not genotoxic. Carcinogenicity studies with ethinylestradiol alone or in combination with various progestogens do not indicate any particular carcinogenic hazard to women when used as indicated for contraception. However it should be noted that sex hormones can advance the growth of certain hormone-dependent tissues and tumours.
Reproductive toxicity studies on fertility, development of the foetus or reproductive ability with ethinylestradiol alone or in combination with progestogens revealed no undesirable effects for humans when used as recommended.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Magnesium stearate
Povidone K-25
Maize starch

Lactose monohydrate

Tablet coating:
Povidone K-90
Macrogol 6000
Talc
Calcium carbonate
Sucrose
Wax montan glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister: PVC/aluminium.

Pack sizes: 1 x 21 tablets, 3 x 21 tablets, 6 x 21 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 126/170/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date of first authorisation: 21st September 2007

Date of last renewal: 25th January 2012

10 DATE OF REVISION OF THE TEXT

July 2012