SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Cyprindiol 2000/35 Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 milligrams cyproterone acetate and 35 micrograms of ethinylestradiol.

For excipients please see section 6.1

3. PHARMACEUTICAL FORM

Coated tablets.

Round, biconvex, yellow sugar-coated tablets with a 5.7mm nominal diameter.

4.1 Therapeutic indications

Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age.
For the treatment of acne, Co - Cyprindiol should only be used after topical therapy or systemic antibiotic treatments have failed.
Since Co - Cyprindiol is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives (see section 4.3).

4.2 Posology and method of administration

First treatment course:
One tablet daily for 21 days, starting on the first day of the menstrual cycle (the first day of menstruation counting as Day I).

Subsequent courses:
Each subsequent course is started 7 tablet-free days after the preceding course.

Duration of Use:
Time to relieve of symptoms is at least three months. The need to continue treatment should be evaluated periodically by the treating physician.

Complete remission of acne is to be expected in nearly all cases, often within a few months, but in particularly severe cases treatment for longer periods may be

necessary before the full benefit is seen. It is recommended that treatment be withdrawn when the acne or hirsutism has completely resolved. Repeat courses of Co - Cyprindiol may be given if the condition recurs.

When the contraceptive action of Co - Cyprindiol is also to be employed, it is essential that the above instructions be rigidly adhered to. Should bleeding fail to occur during the tablet-free interval, the possibility of pregnancy must be excluded before the next pack is started.

When changing from an oral contraceptive and relying on the contraceptive action of Co Cyprindiol Coated Tablets, the instructions given below should be followed:

Changing from 21-day combined oral contraceptives:
The first tablet of Co - Cyprindiol should be taken on the first day immediately after the end of the previous oral contraceptive course. Additional contraceptive precautions are not required.

Changing from a combined Every Day Pill (28 day tablets):
The first Co - Cyprindiol tablet should be taken the day after taking the last active tablet from the Every Day Pill pack. Additional contraceptive precautions arc not then required.

Changing from a progestogen-only pill (POP):
The first tablet of Co - Cyprindiol should be taken on the first day of bleeding, even if a POP has already been taken on that day. Additional contraceptive precautions are not then required. The remaining progestogen-only pills should be discarded.

Postpartum and post-abortum use:
After pregnancy, Co - Cyprindiol can be started 21 days after a vaginal delivery, provided the patient is fully ambulant and there are no puerperal complications. Additional contraceptive precautions will be required for the first 7 days of pill taking. Since the first postpartum ovulation may precede the first bleeding, another method of contraception should be used in the interval between childbirth and the first course of tablets.

After a first-trimester abortion, Co - Cyprindiol may be started immediately and no additional contraceptive precautions are required.

Special circumstances requiring additional contraception

Incorrect administration:
A single delayed tablet should be taken as soon as possible, and if this is within 12 hours of the correct time, contraceptive protection is maintained. With longer delays, additional contraception is needed. Only the most recently delayed tablet should be taken, earlier missed tablets being omitted. Additional non-hormonal methods of contraception (except the rhythm or temperature methods) should be used for the next 7 days, while the next 7 tablets are being taken. Also, if tablet(s) have been missed during the last 7 days of a pack, there should be no break before the next pack is started. In this situation, a withdrawal bleed should not be expected until the end of the second pack. Some breakthrough bleeding may occur on tablet taking days but this is not clinically significant. If the patient does not have a withdrawal bleed during the tablet- free interval following the end of the second pack, the possibility of pregnancy must be ruled out before starting the next pack.

Gastrointestinal upset:
Vomiting or diarrhoea may reduce the efficacy of oral contraceptives by preventing full absorption. Tablet taking from the current pack should be continued and additional non hormonal methods of contraception (except the rhythm or temperature methods) should be used during the gastrointestinal upset, and for 7 days following the upset. If these 7 days overrun the end of a pack, the next pack should be started without a break. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed during this period the possibility of pregnancy must be filled out before starting the next pack. Other methods of contraception should be considered if the gastrointestinal disorder is likely to be prolonged.

4.3 Contraindications

1. Pregnancy or lactation

2. Severe disturbances of liver function, jaundice or persistent itching during a previous pregnancy, Dubin-Johnson syndrome, Rotor syndrome, previous or existing liver tumours.

3. Existing or previous arterial or venous thrombotic or embolic processes, conditions which predispose to them e.g. disorders of the clotting processes, valvular heart disease and atrial fibrillation.

4. Sickle cell anaemia.

5. Mammary or endometrial carcinoma or a history of these conditions.

6. Severe diabetes mellitus with vascular changes.

7. Disorders of lipid metabolism.

8. History of herpes gestationis.

9. Deterioration of otosclerosis during pregnancy.

10. Undiagnosed abnormal vaginal bleeding.

11. Hypersensitivity to any of the components of Co - Cyprindiol Coated Tablets.

12. Concomitant use with another hormonal contraceptive (see section 4.1)

13. Venous thrombosis present or in history (deep venous thrombosis, pulmonary embolism)

14. Arterial thrombosis present or in history (e.g. myocardial infarction) or prodromal conditions (e.g. angina pectoris and transient ischaemic attack).

15. Presence or history of cerebrovascular accident

16. The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis (see section 4.4) such as:

- diabetes mellitus with vascular symptoms

- severe hypertension
- severe dyslipoproteinaemia

17. 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)

4.4. Special warning and precautions for use

Warnings:
Like many other steroids, the combination of cyproterone acetate and ethinylestradiol has been found to cause an increase in the incidence of tumours (including carcinoma) in the liver of rats, when given in very high doses and for the majority of the animal's life-span. The relevance of this finding to humans is unknown.

In rare cases benign and, in even rarer cases, malignant liver tumours leading to life-threatening intra-abdominal haemorrhage in isolated cases, have been observed after the use of hormonal substances such as those contained in Co - Cyprindiol Coated Tablets. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour sbould be included in the differential diagnosis.

Co - Cyprindiol is composed of the progestogen cyproterone acetate and the oestrogen ethinylestradiol and is administered for 21 days of a monthly cycle. It has a similar composition to that of a combined oral contraceptive (COC).

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 4.2).

Co - Cyprindiol has many properties in common with combined oral contraceptives (COC). which must not be taken during treatment with Co - Cyprindiol Tablets. Statistical evidence suggests that users of combined oral contraceptives experience higher incidence of venous thromboembolism, arterial thrombosis, including cerebral and myocardial infarction, and subarachnoid haemorrhage, more often than non-users. Full recovery from such disorders does not always occur, and in a few cases they are fatal. The frequency of these disorders in users of the modem low-dose pills is unknown, but they are thought to occur less often than with older pills.

Certain factors may entail some risk of thrombosis e.g. smoking, obesity, varicose veins,

cardiovascular diseases, diabetes and migraine. The risk of arterial thrombosis associated with combined oral contraceptives increases with age, and cigarette smoking aggravates this risk. In addition, if there is a family history of thromboembolic diseases at a young age (e.g. deep vein thrombosis, heart attack or stroke), disturbances of the coagulation system must be ruled out before Co - Cyprindiol is prescribed. The suitability of Co - Cyprindiol should be judged according to the severity of such conditions in individual cases, and should be discussed with the patient before taking it.

The evidence from numerous epidemiological studies have reported that combined oral contraceptives offer substantial protection against both ovarian and endometrial cancer. However other studies have reported an increased risk of cervical cancer in long-term users of combined oral contraceptives. There continues to be controversy over the extent to which this is attributable to the confounding effects of sexual behaviour and other factors.

Epidemiological studies have reported a slightly increased relative risk of having breast cancer diagnosed in women who were currently using combined oral contraceptives. The additional breast cancers diagnosed in current users of COCs or in women who have used COCs in the last ten years are more likely to be localised to the breast than those in women who never used COCs.

Breast cancer is rare among women under 40 years of age whether or not they take COCs. Whilst this background risk increases with age, the excess number of breast cancer diagnosed in current and recent COC users is small in relation to the overall risk of breast cancer.

The most important risk factor for breast cancer in COC users is the age women discontinue the COC*;* the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping COC use such that by 10 years there appears to be no excess risk.

The possible increased risk of breast cancer should be discussed with the user and weighed against the benefits of COCs as they offer substantial protection against the risk of developing certain other cancers (e.g, ovarian and endometrial cancer).

The possibility cannot be ruled out that certain chronic diseases may occasionally deteriorate during the use of Co - Cyprindiol (see Precautions).

Reasons for stopping Co - Cyprindiol immediately:

1. Occurrence, or exacerbation of migraines, headaches or unusually frequent or severe headaches.

2. Sudden disturbances of vision or hearing or other perceptual disorders.

3. First signs of thrombophlebitis or thromboembolic symptoms (e.g. unusual pains in or swelling of the leg(s), stabbing pains on breathing or coughing for no apparent reason). Pain and tightness in the chest.

4. Six weeks before an elective major operation (e.g. abdominal, orthopaedic), any surgery to the legs, medical treatment for varicose veins or prolonged immobilisation, e.g. after accidents or surgery. Co - Cyprindiol should not be restarted until 2 weeks after full ambulation. In case of emergency surgery, thrombotic prophylaxis is usually indicated e.g. subcutaneous heparin.

5. Onset of jaundice, hepatitis or itching of the whole body.

6. Increase in epileptic seizures.

7. Significant rise in blood pressure.

8. Onset of severe depression.

9. Severe upper abdominal pain or liver enlargement.

10. Clear exacerbation of conditions known to be capable of deteriorating during oral contraception or pregnancy.

11. Pregnancy. It has been suggested by some investigations that oral contraceptives taken in early pregnancy may slightly increase the risk of foetal malformations. Other investigations have failed to support these findings. The possibility therefore cannot be excluded, but the risk is very small.

Precautions:

Assessment of women prior to starting oral contraceptives (and at regular intervals thereafter) should include a personal and family medical history. Physical examination should he guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for this product. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and, if judged appropriate by the clinician, breast, abdominal and pelvic examination including cervical cytology.

If any of the conditions/risk factors mentioned below is present, the benefits of the use of Co- Cyprindiol should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using Co- Cyprindiol. 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 the use of Co- Cyprindiol should be discontinued.

Diabetes mellitus or a tendency towards diabetes mellitus (e.g. unexplained glycosuria).

Hypertension, varicose veins, a history of phlebitis, otosclerosis, multiple sclerosis, epilepsy, porphyria, tetany, disturbed liver function, Sydenham's chorea, renal dysfunction, family history of clotting disorders, obesity, family history of breast cancer and patient history of benign breast disease, systemic lupus erythematosus, uterine fibroids, an intolerance to contact lenses, migraine, gall-stones, cardiovascular diseases, chloasma, asthma, or any disease that is prone to worsen during pregnancy.

Post- marketing reports of severe depression have been received in association with the use of Co-Cyprindiol. Co- Cyprindiol should be discontinued and other methods of contraception introduced if severe depression develops. Patients with a history of depression require careful supervision during treatment with Co- Cyprindiol. Discontinuation should be considered in the event of deterioration of existing depression or the appearance of depression for the first time.”

The use of ultraviolet lamps, for the treatment of acne, or prolonged exposure to sun light, increases the risk of the deterioration of chloasma.

Some women may experience amenorrhoea or oligomenorrhoea after discontinuation of

Co-Cyprindiol , especially when these conditions existed prior to use. Women should be

informed of this possibility.

Circulatory disorders

The use of Co-Cyprindiol 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 starts Co-Cyprindiol or when restarting or switching after a pill-free interval of at least a month. Venous thromboembolism can be fatal in 1-2% of cases.

Epidemiological studies have shown that the incidence of VTE is 1.5 to 2 times higher in users of Co-Cyprindiol 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 Co-Cyprindiol 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 hormonal contraceptive users.

Symptoms of venous or arterial thrombosis or of a cerebrovascular accident can include: unusual 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 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 of age should be strongly advised not to smoke if they wish to use Co-Cyprindiol);
- a positive family history (i.e. venous thromboembolism 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;
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation. Antithrombotic treatment should be considered if the use of Co-Cyprindiol has not been discontinued in advance.
- obesity (body mass index over 30 kg/m^2).

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 of age should be strongly advised not to smoke if they wish to use Co-Cyprindiol);
- dyslipoproteinemia;
- obesity (body mass index over 30 kg/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.

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

The increased risk of thromboembolism in the puerperium must be considered (for information on 'Pregnancy and lactation' see section 4.6).

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

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

4.5. Interaction with other medicinal products and other forms of interaction

Hepatic enzyme inducers such as barbiturates, primidone, phenobarbital, phenytoin, phenylbutazone, rifampicin, carbamazepine and griseofulvin can impair the contraceptive efficacy of Co - Cyprindiol Coated Tablets. For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be used.

The use of antibiotics may also reduce the contraceptive efficacy of Co – Cyprindiol .

Women receiving short courses of enzyme inducers and broad spectrum antibiotics should take additional, non-hormonal (except rhythm or temperature method) contraceptive precautions during the time of concurrent medication and for 7 days afterwards. If these 7 days overrun the end of a pack, the next pack should be started without a break. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

The possibility cannot be ruled out that oral tetracyclines, if used in conjunction with Co - Cyprindiol may reduce its contraceptive efficacy. When drugs of these classes are being taken it is, therefore, advisable to use additional non-hormonal methods of contraception (except the rhythm or temperature methods) since an extremely high degree of protection must be provided when Co - Cyprindiol is being taken. With rifampicin, additional contraceptive precautions should be continued for 4 weeks after treatment stops, even if only a short course was administered.

The requirement for oral antidiabetics or insulin can change as a result of the effect on glucose tolerance.

The herbal remedy St John's wort (Hypericum perforatum) should not be taken concomitantly with Co - Cyprindiol as this could potentially lead to a loss of contraceptive effect.

4.6 Pregnancy and lactation

Pregnancy is an absolute contraindication for treatment with Co - Cyprindiol and must be excluded before such treatment is begun.

Animal studies have revealed that feminisation of male foetuses may occur if cyproterone acetate is administered during the phase of embryogenesis when differentiation of the external genitalia occurs. Although these findings are not necessarily relevant to man, pregnancy is an absolute contraindication for treatment with Co - Cyprindiol Coated Tablets, and must be excluded before treatment is begun.

Lactation is contraindicated.

4.7 Effects on ability to drive and use machines

None known.

4.8. Undesirable effects

In rare cases, headaches, gastric upsets, nausea, vomiting, breast tenderness, changes in body weight, changes in libido and depressive moods can occur.

There is an increased risk of thromboembolism for all women who use Co - Cyprindiol (see section 4.4).

Vascular Disorders Rare (≥ 1/10,000 to < 1/1000): Thromboembolism

The following serious adverse events have been reported in women using Co - Cyprindiol, which are discussed in section 4.4 Special warning and precautions for use:

- Venous thromboembolic disorders
- Arterial thromboembolic disorders

Post-marketing reports of severe depression have been received in association with the use of Co- Cyprindiol (see section 4.4 Special warnings and precautions for use).

Use of Co - Cyprindiol can sometimes cause chloasma in predisposed women, which is exacerbated by exposure to sunlight. Such women should avoid prolonged exposure to sunlight.

Individual cases of poor tolerance of contact lenses have been reported with use of oral contraceptives. Contact lens wearers who develop changes in lens tolerance should be assessed by an ophthalmologist.

Menstrual changes:

1. Reduction of menstrual flow - this is not abnormal and is to be expected in some patients.

2. Missed menstruation- occasionally withdrawal bleeding may not occur at all. If the tablets have been taken correctly, pregnancy is unlikely. Should bleeding fail to occur during the tablet-free interval the possibility of pregnancy must be excluded before the next pack is started.

3. Intermenstrual bleeding - "spotting" or heavier "breakthrough bleeding" can sometimes occur during tablet taking, especially in the first few cycles, but normally cease spontaneously. Co - Cyprindiol should be continued even if irregular bleeding occurs.
   If irregular bleeding is persistent, appropriate diagnostic measures to exclude an organic cause are indicated and may include curettage. This also applies when spotting occurs at regular intervals in several consecutive cycles or occurs for the first time after long use of Co - Cyprindiol Coated Tablets.

Effect on blood chemistry:
The use of oral contraceptives may influence the results of certain laboratory tests including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Laboratory staff should therefore be informed about oral contraceptive use when laboratory tests are requested.

Refer to section 4.4 for additional information.

4.9 Overdose

Overdose may cause nausea, vomiting and, in females, withdrawal bleeding.

There are no specific antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

ATC code: G03HB01

5.1 Pharmacodynamic properties

Co - Cyprindiol blocks androgen-receptors. It also reduces androgen synthesis both by a negative feedback effect on the hypothalamo-pituitiary-ovarian systems and by the inhibition of androgen-synthesising enzymes.

Although Co - Cyprindiol also acts as an oral contraceptive, it is not recommended in women solely for contraception, but should be reserved for those women requiring treatment for the androgen-dependent skin conditions described.

5.2 Pharmacokinetic properties

Cyproterone acetate:
Following oral administration cyproterone acetate is completely absorbed over a wide dose range. The ingestion of 2mg cyproterone in combination with 0.035mg of ethinylestradiol gave a maximum serum level of 15ng cyproterone acetate/ml at 1.6 hours. Thereafter drug serum levels decrease in two disposition phases characterised by half-lives of 0.8 hours and 2.3 days. The total clearance of cyproterone acetate from serum was determined to be 3.6 ml/min/kg. Cyproterone acetate is metabolised by various pathways including hydroxylations and conjugations. The main metabolite in human plasma is the 15-hydroxy derivative.

Some of the dose was excreted unchanged with the bile fluid. Most is excreted in the form of metabolites at a urinary to biliary ratio of 3:7. The renal and biliary excretion was determined to proceed with half-life of 1.9 days. Metabolites from plasma were eliminated at a similar rate (half-life of 1.7 days). Cyproterone acetate is almost exclusively bound to plasma albumin only about 3.5 - 4.0% of total drug levels are present unbound. Because protein binding is non-specific, changes in sex hormone binding globulin (SHBG) levels do not affect cyproterone acetate pharmacokinetics.

According to the long half-life of the terminal disposition phase from plasma (serum) and the daily intake, cyproterone acetate accumulates during one treatment cycle. Mean maximum drug serum levels increased from 15ng/ml (day 1) to 21ng/ml and 24ng/ml at the end of the treatment cycles 1 and 3 respectively. The area under the concentration versus time profile increased 2.2 fold (end of cycle 1) and 2.4 fold (end of cycle 3). Steady state conditions

were reached after about 16 days. During long term treatment cyproterone acetate accumulates over treatment cycles by a factor of 2.

The absolute bioavailability of cyproterone acetate is almost complete (88% of dose). The relative bioavailability of cyproterone acetate (in combination with 0.035mg of ethinylestradiol) was 109% when compared to an aqueous microcrystalline suspension.

Ethinylestradiol:
Orally administered ethinylestradiol is rapidly and completely absorbed. Following ingestion of 0.035mg of ethinylestradiol in combination with 2mg of cyproterone, maximum drug serum levels of about 80pg/ml are reached at 1.7 hours. Thereafter ethinylestradiol plasma levels decrease in two phases characterised by half-lives of 1 - 2 hours and about 20 hours. For analytical reasons these parameters can only be calculated for higher dosages.

For ethinylestradiol an apparent volume of distribution of about 5 l/kg and a metabolic clearance rate from plasma of about 5 ml/min/kg were determined.

Ethinylestradiol is highly, but non-specifically bound to serum albumin only 2% of the drug levels are present unbound. During absorption and first liver passage ethinylestradiol is metabolised resulting in a reduced absolute and variable oral bioavailability. Unchanged drug is not excreted. Ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6 with a half-life of about 1 day.

According to the half-life of the terminal disposition phase from plasma and the daily ingestion, steady state plasma levels are reached after 3 - 4 days and are higher by 30 - 40% as compared to a single dose. The relative bioavailability (reference: aqueous microcrystalline suspension) of ethinylestradiol was almost complete.

The systemic bioavailability of ethinylestradiol might be influenced in both directions by other drugs. There is, however, no interaction with high doses of vitamin C.

Ethinylestradiol induces the hepatic synthesis of SHBG and corticosteroid binding globulin (CBG) during continuous use. The extent of SHBG induction, however, is dependent upon the chemical structure and dose of the co-administered progestin.

5.3 Preclinical safety data

There are no preclinical safety data which could be of relevance to the prescriber and which are not already included in other relevant sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, maize starch, povidone K25, talcum, magnesium stearate, sucrose, calcium carbonate, polyethylene glycol 6000, Povidone K90 titanium dioxide (E 171), glycerol 85%, montan glycol wax, iron oxide pigment.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the original package

6.5 Nature and contents of container

PVC blister (250µm) and aluminium foil (20µm) packs or PVC/PVDC blister (40 gsm) and aluminium foil (20µm) each containing 21 tablets. Each carton contains either 1 or 3 blister strips.

6.6. Instructions for use and handling

Keep out of sight and reach of children.

7 MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PL 15764/0011

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