

**CO-CYPRINDIOL 2000/35 COATED TABLETS
PL 14894/0413**

UKPAR

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**CO-CYPRINDIOL 2000/35 COATED TABLETS
PL 14894/0413**

LAY SUMMARY

The MHRA granted Ranbaxy (UK) Limited Marketing Authorisations (licences) for the medicinal products Co-Cyprindiol 2000/35 Coated Tablets on 27th September 2006. This product to be sold on prescription only (POM) contains cyproterone acetate and ethinylestradiol, and is used for use only in women for the treatment of severe acne, which has been unaffected by prolonged oral antibiotic therapy and moderately severe hirsutism.

The active ingredients cyproterone acetate and ethinylestradiol act by blocking the effects of hormones called androgens on the skin.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Co-Cyprindiol 2000/35 Coated Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

**CO-CYPRINDIOL 2000/35 COATED TABLETS
PL 14894/0413**

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products Co-Cyprindiol 2000/35 Coated Tablets (PL 14894/0413) to Ranbaxy (UK) Limited on 27th September 2006. The products are available as prescription-only medicines (POM).

The application was submitted as a simple abridged application according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Co-Cyprindiol 2000/35 Tablets (PL 17926/0004), which was originally approved on 25th July 2003 to the marketing authorisation holder Stiefel Laboratories (UK) Limited (PL 00174/0221) before undergoing a change of ownership to Helm Pharmaceuticals GmbH on 23rd January 2004.

No new data was submitted nor was it necessary for these simple applications, as the data is identical to that of the previously granted cross-reference product. As the cross-reference products were granted prior to the introduction of current legislation, no PARs were generated for them.

The active ingredients cyproterone acetate and ethinylestradiol act as androgen blockers and are indicated in the treatment of severe acne, refractory to prolonged oral antibiotic treatment, and moderately severe hirsutism.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 14894/0413

PROPRIETARY NAME: Co-Cyprindiol 2000/35 Coated Tablets

ACTIVE(S): Cyproterone acetate and Ethinylestradiol

COMPANY NAME: Helm Pharmaceuticals GmbH

E.C. ARTICLE: Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC

LEGAL STATUS: POM

1. INTRODUCTION

This is a simple, piggy back application for Co-Cyprindiol 2000/35 Coated Tablets submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Ranbaxy (UK) Limited, 95 Park Lane, Mayfair, London, W1K 7TE.

The application cross-refers to Co-Cyprindiol 2000/35 Tablets (PL 17926/0004), which was originally approved on 25th July 2003 to the marketing authorisation holder Stiefel Laboratories (UK) Limited (PL 00174/0221) before undergoing a change of ownership to Helm Pharmaceuticals GmbH on 23rd January 2004.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name of the product is Co-Cyprindiol 2000/35 Coated Tablets. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains cyproterone acetate (equivalent to 2000 microgrammes) and ethinylestradiol (equivalent to 35 microgrammes). It is to be stored in PVC or PVC/PVDC blisters and heat-sealable aluminium foil. The proposed shelf-life (36 months) and storage conditions (none) are consistent with the details registered for the cross-reference product.

2.3 Legal status

On approval, the products will be available by prescription that may be renewed.

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation Holder is Ranbaxy (UK) Limited, 95 Park Lane, Mayfair, London, W1K 7TE.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification

The proposed finished product specification is in line with the details registered for the cross-reference product.

2.9 Drug substance specification

The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance

No materials of animal or human origin are included in the product. This is consistent with the cross reference product.

3. EXPERT REPORTS

The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts' CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The proposed summary is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/CARTON

PIL

The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

Carton and blister

The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS

The data submitted with the application are acceptable. A Marketing Authorisation should be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

As this is a duplicate application, no new clinical data have been supplied and none are required.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application are consistent with that previously assessed for the cross-reference product and as such have been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

These applications are identical to a previously granted application for Co-Cyprindiol 2000/35 Tablets (PL 17926/0004).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products which, in turn, have been shown to be interchangeable with the innovator products.

Extensive clinical experience with sodium chloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

**CO-CYPRINDIOL 2000/35 COATED TABLETS
PL 14894/0413**

STEPS TAKEN FOR ASSESMENT

| | |
|---|---|
| 1 | The MHRA received the marketing authorisation application on 23/12/2004. |
| 2 | Following standard checks and communication with the applicant the MHRA considered the application valid on 24/01/2005. |
| 3 | Following assessment of the application the MHRA requested further information on 26/05/2005 and 30/11/2005. |
| 4 | The applicant responded to the MHRA's requests, providing further information on 14/07/2005 and 26/09/2006 |
| 5 | The application was determined on 27/09/2006 |

**CO-CYPRINDIOL 2000/35 COATED TABLETS
PL 14894/0413**

STEPS TAKEN AFTER ASSESSMENT

| Date submitted | Application type | Scope | Outcome |
|-----------------------|-------------------------|--------------|----------------|
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CO-CYPRINDIOL 2000/35 COATED TABLETS

PL 14894/0413

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Cyprindiol 2000/35 Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2000 micrograms 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 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-Cyprindiol 2000/35 Coated Tablets is indicated for use only in women for the treatment of (a) severe acne, refractory to prolonged oral antibiotic therapy; (b) moderately severe hirsutism.

Although Co-Cyprindiol 2000/35 Coated Tablets also acts as an oral contraceptive, it is not recommended solely for contraception, but should be reserved for women requiring treatment for the androgen-dependent skin conditions described.

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 may be necessary before the full benefit is seen. It is recommended that treatment be withdrawn 3 to 4 cycles after the indicated condition(s) has/have completely resolved and that Co-Cyprindiol is not continued solely to provide oral contraception. Repeat courses of Co-Cyprindiol may be given if the androgen-dependent condition(s) recur.

4.2 Posology and method of administration

Co-Cyprindiol inhibits ovulation and thereby prevents conception. The contraceptive action starts with the intake on the first day of the cycle. Contraception is also effective during the 7 tablet-free days. Concomitant use of any other hormonal pregnancy prevention method is not allowed as this will expose the patient to an excessive dose of hormones and is not necessary for effective contraception.

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 1).

Women with amenorrhoea should start therapy immediately. In this case the first day of tablet intake is considered as the first day of the cycle.

Subsequent courses:

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

When the contraceptive action of Co-Cyprindiol 2000/35 Coated Tablets 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 2000/35 Coated Tablets, the instructions given below should be followed:

Changing from 21-day combined oral contraceptives:

The first tablet of Co-Cyprindiol 2000/35 Coated Tablets 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 oral contraceptive (28 day tablets):

The first Co-Cyprindiol 2000/35 Coated Tablets should be taken the day after taking the last active tablet from the Every Day oral contraceptive pack. Additional contraceptive precautions are not then required.

Changing from a progestogen-only oral contraceptive (POP):

The first tablet of Co-Cyprindiol 2000/35 Coated Tablets 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 oral contraceptive should be discarded.

Post-partum and post-abortion use:

After pregnancy, Co-Cyprindiol 2000/35 Coated Tablets 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 taking the oral contraceptive. Since the first post-partum ovulation may precede the first bleeding, another method of contraception should be used in the interval between childbirth and the first course of tablets. Lactation is contraindicated with Co-Cyprindiol.

After a first-trimester abortion, Co-Cyprindiol 2000/35 Coated Tablets 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 can be done 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.

Gastro-intestinal 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 gastro-intestinal 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 ruled out before starting the next pack. Other methods of contraception should be considered if the gastro-intestinal 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. Personal or family history of confirmed, idiopathic venous or arterial thrombosis (VTE) (where a family history refers to VTE in a sibling or parent at a relatively early age).
4. Current venous thrombotic or embolic processes.
5. Existing or previous arterial thrombotic or embolic processes.
6. Severe hypertension.

7. The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see section 4.4).
8. Sickle-cell anaemia.
9. Mammary or endometrial carcinoma or a history of these conditions.
10. Severe diabetes mellitus with vascular changes.
11. Disorders of lipid metabolism.
12. History of herpes gestationis.
13. Deterioration of otosclerosis during pregnancy.
14. Undiagnosed abnormal vaginal bleeding.
15. Hypersensitivity to any of the components of Co-Cyprindiol 2000/35 Coated Tablets
16. Migraine with focal aura

4.4 Special warnings and precautions for use

Warnings: Like many other steroids, Co-Cyprindiol 2000/35 Coated Tablets, when given in very high doses and for the majority of the animal's life-span, has been found to cause an increase in the incidence of tumours, including carcinoma, in the liver of rats. The relevance of this finding to humans is unknown.

In rare cases benign and in even rarer cases malignant liver tumours leading in isolated cases to life-threatening intra-abdominal haemorrhage have been observed after the use of hormonal substances such as those contained in Co-Cyprindiol 2000/35 Coated Tablets. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential diagnosis.

Animal studies have revealed that feminisation of male foetuses may occur if cyproterone acetate is administered during the phase of embryogenesis at which differentiation of the external genitalia occurs. Although the results of these tests are not necessarily relevant to man, the possibility must be considered that administration of Co-Cyprindiol 2000/35 Coated Tablets to women after the 45th day of pregnancy could cause feminisation of male foetuses. It follows from this that pregnancy is an absolute contra-indication for treatment with Co-Cyprindiol 2000/35 Coated Tablets, and must be excluded before such treatment is begun.

Co-Cyprindiol 2000/35 Coated Tablets is composed of the progestogen cyproterone acetate and the oestrogen ethinylestradiol and is administered for 21 days of a monthly cycle. It therefore has a similar composition to that of a combined oral contraceptive (COC). The use of any COC or Co-Cyprindiol 2000/35 Coated Tablets carries an increased risk for venous thromboembolism (VTE), including deep venous thrombosis and pulmonary embolism, 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 per 100,000 pregnancies.

Full recovery from such disorders does not always occur; VTE is fatal in 1-2% of cases.

Epidemiological studies have shown that the incidence of VTE in users of oral contraceptives with low oestrogen content (< 50 µg ethinylestradiol) is up to 40 cases per 100,000 women-years. This compares with 5-10 cases per 100,000 women-years for non-users.

Certain factors may increase the risk of venous thrombosis e.g. severe obesity (body mass index > 30kg/m²), increasing age, a genetic predisposition to clotting or a personal or family history of confirmed, idiopathic VTE (where family history refers to VTE in a sibling or parent at a relatively early age, see contraindications section 4.3). In addition, the risk of VTE may be temporarily increased by prolonged immobilisation, major surgery, any surgery to the legs, or major trauma (see "Reasons for stopping Co-Cyprindiol 2000/35 Coated Tablets immediately").

There is some epidemiological evidence that the incidence of VTE is higher in users of Co-Cyprindiol 2000/35 Coated Tablets when compared to users of COCs with low oestrogen content (< 50µg).

The user group of Co-Cyprindiol 2000/35 Coated Tablets as a treatment for severe acne or moderately severe hirsutism 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 COCs with an increased risk for arterial (myocardial infarction, transient ischaemic attack) thromboembolism. Certain factors such as smoking, obesity, cardiovascular disease, hypertension, diabetes and migraine may increase the risk of arterial thromboembolism. The risk of arterial thrombosis associated with oral contraceptives increases with age, and this risk is aggravated by cigarette smoking.

Numerous epidemiological studies have been reported on the risks of ovarian, endometrial, cervical and breast cancer in women using combined oral contraceptives. The evidence is clear that combined oral contraceptives offer substantial protection against both ovarian and endometrial cancer.

An increased risk of cervical cancer in long-term users of combined oral contraceptives has been reported in some studies, but there continues to be controversy about the extent to which this is attributable to the confounding effects of sexual behaviour and other factors.

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 combined oral contraceptives (COCs). 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 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 diagnoses 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.

The possible increase in risk of breast cancer should be discussed with the user and weighed against the benefits of COCs taking into account the evidence that 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 2000/35 Coated Tablets (see Precautions)

Reasons for stopping Co-Cyprindiol 2000/35 Coated Tablets immediately:

1. Occurrence for the first time, or exacerbation, of migrainous headaches or unusually frequent or unusually 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). Feeling of 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. Do not restart 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, 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 worsening of conditions known to deteriorate during use of hormonal contraception or during pregnancy.
11. Pregnancy is a reason for stopping immediately because 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 it is certain that if a risk exists at all, it is small.

Precautions:

Assessment of women prior to starting oral contraceptives (and at regular intervals thereafter) should include a personal and family medical history of each woman. Physical examination should be 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.

The following conditions require strict medical supervision during medication with oral contraceptives. Deterioration or first appearance of any of these conditions may indicate that Co-Cyprindiol 2000/35 Coated Tablets 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, history of clinical depression, 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.

Benign endometrial tumour, endometriosis, mastopathia and also, women older than 40 years and women with a history of phlebitis and tendency towards diabetes mellitus should be supervised.

It should be borne in mind that the use of ultraviolet lamps, for the treatment of acne, or prolonged exposure to sunlight, increases the risk of the deterioration of chloasma.

Some women may experience amenorrhoea or oligomenorrhoea after discontinuation of Co-Cyprindiol 2000/35 Coated Tablets, especially when these conditions existed prior to use. Women should be informed of this possibility.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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 2000/35 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 2000/35 Coated Tablets.

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 2000/35 Coated Tablets 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 2000/35 Coated Tablets 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 2000/35 Coated Tablets as this could potentially lead to a loss of contraceptive effect.

4.6 Pregnancy and lactation

Pregnancy is an absolute contra-indication for treatment with Co-Cyprindiol 2000/35 Coated Tablets 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 contra-indication for treatment with Co-Cyprindiol 2000/35 Coated Tablets, and must be excluded before treatment is begun.

Use of Co-Cyprindiol 2000/35 Coated Tablets is contraindicated during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or operate machines have been performed.

4.8 Undesirable effects

In this section undesirable effects are defined as follows:

Very common $\geq 1/10$; common $\geq 1/100$ to $< 1/10$; uncommon $\geq 1/1000$ to $\leq 1/100$; rare $\geq 1/10,000$ to $\leq 1/1,000$; very rare $\leq 1/10,000$, not known (cannot be estimated from the available data).

There is an increased risk of venous thromboembolism for all women who use Co-Cyprindiol 2000/35 Coated Tablets. For more information see section 4.4.

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

Use of Co-Cyprindiol 2000/35 Coated Tablets 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:

Reduction of menstrual flow - this is not abnormal and is to be expected in some patients. Indeed, it may be beneficial where heavy periods were previously experienced.

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.

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 2000/35 Coated Tablets 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 2000/35 Coated Tablets 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 “Special warnings and special precautions for use” for additional information.

| | |
|--------------------|---|
| Common (>1/100) | General: Change in body-weight, headache, migraine CNS: Depressive moods, change in libido Endocrine: Breast tenderness Gastrointestinal: Nausea, vomiting Urogenital: Spotting or breakthrough Bleeding, dysmenorrhoea |
| Less common | General: Fluid retention Circulation: Elevation of blood pressure Urogenital: Reduction of menstrual flow |
| Rare (<1/1000) | Circulation: Venous thromboembolism (deep venous thrombosis, pulmonary embolism. Arterial thromboembolism (myocardial infarction, ischaemic attack). Endocrine: Decreased glucose tolerance, elevated blood sugar, increased insulin need, pancreatitis Skin: Chloasma, pruritus, alopecia Liver: Reversible elevation of transaminase levels, hepatitis, intrahepatic cholestasis, gallstones, benign liver adenoma, focal nodular hyperplasia Eyes: Decreased epiphora, reduced tolerance for contact lens wear Investigations: Alterations in biochemical parameters of thyroid, adrenal and renal function, plasma levels of carrier proteins and lipid/lipoprotein fractions, parameters of coagulation and fibrinolysis. |

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiandrogens and estrogens

ATC code: G03HB01

Co-Cyprindiol 2000/35 Coated Tablets blocks androgen-receptors. It also reduces androgen synthesis both by a negative feedback effect on the hypothalamo-pituitary-ovarian systems and by the inhibition of androgen-synthesising enzymes.

Although Co-Cyprindiol 2000/35 Coated Tablets 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

Tablet Cores
Lactose monohydrate
Maize starch
Povidone K25
Talcum
Magnesium stearate (E572)

Tablet coating

Sucrose
Calcium carbonate (E170)
Talcum
Titanium dioxide (E171)
Povidone K90
Macrogol 6000
Glycerol 85% (E422)

Iron oxide pigment (E172)
Montan glycol wax

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.

Pack size of 63 Tablets.

6.6 Special precautions for disposal
Keep out of sight and reach of children.

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Ltd
95 Park Lane, Mayfair,
London W1K 7TE

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0413

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/09/2006

10 DATE OF REVISION OF THE TEXT
27/09/2006

CO-CYPRINDIOL 2000/35 COATED TABLETS PL 14894/0413

PATIENT INFORMATION LEAFLET



PATIENT INFORMATION LEAFLET

Co-Cyprindiol 2000/35 Coated Tablets

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours

In this leaflet:

1. **What Co-Cyprindiol 2000/35 Coated Tablets are and what are they used for**
2. **Before you take Co-Cyprindiol 2000/35 Coated Tablets**
3. **How to take Co-Cyprindiol 2000/35 Coated Tablets**
4. **Possible side effects**
5. **Storing Co-Cyprindiol 2000/35 Coated Tablets**

The name of your medicine is Co-Cyprindiol 2000/35 Coated Tablets

The active substances are cyproterone acetate and ethinylestradiol.

Co-Cyprindiol 2000/35 Coated Tablets contains some inactive ingredients: these are Lactose monohydrate, maize starch, povidone, talcum, magnesium stearate (E 572), sucrose, calcium carbonate (E 170), titanium dioxide (E 171), macrogol 6000, glycerol 85% (E 422), iron oxide pigment (E 172) and montan glycol wax.

Marketing Authorisation Holder: Ranbaxy (UK) Limited, 95 Park Lane, Mayfair, London W1K 7TE.

Manufacturer: Haupt Pharma Münster GmbH, Schleibrüggenkamp 15, 48159 Münster, Germany.

1. **What Co-Cyprindiol 2000/35 Coated Tablets are and what are they used for**

Co-Cyprindiol 2000/35 Coated Tablets are round, yellow coloured tablets and are available in packs of 63 tablets.

Co-Cyprindiol 2000/35 Coated Tablets are only for use in women. It works to block the action of a certain type of hormone (androgen) and also reduces androgen production.

It also thickens the mucus in the neck of the womb preventing sperm getting through and makes the lining of the womb unsuitable for an egg to grow on.

Co-Cyprindiol 2000/35 Coated Tablets are used for treating severe acne of the skin that has not improved even after long-term use of oral antibiotics. It is also used to treat excessive hair growth on the face and body.

Co-Cyprindiol 2000/35 Coated Tablets work by blocking the effect of hormones called androgens on the skin. Your medicine also reduces the amount of androgen produced by the ovaries. Androgens stimulate the oily substance that gives you greasy skin. This can lead to blockage of the grease glands, which can then become infected and inflamed causing acne spots. Androgens may also stimulate growth of hair on the face and body.

Co-Cyprindiol 2000/35 Coated Tablets are also an effective contraceptive so while you are taking this medicine, you will not need to take any other oral contraceptive pill.

2. **Before you take Co-Cyprindiol 2000/35 Coated Tablets**

- **Do not take Co-Cyprindiol 2000/35 Coated Tablets if:**
 - you have previously had an allergic reaction to Co-Cyprindiol or to any of the tablet ingredients listed above (An allergic reaction may include rash, itching, swelling of face, lips, tongue, or hands/feet or breathing difficulties)
 - you are pregnant or think you may be pregnant
 - you are breast feeding
 - you or any member of your close family (parent, brother, sister) has or has ever had blood clots in the legs, lungs, eyes, or anywhere else
 - you or any member of your close family has had a heart attack or stroke, or have any medical condition which makes you more at risk of developing blood clots
 - abnormal red blood cells (sickle-cell anaemia)
 - disorders of blood fat (lipid) metabolism
 - cancer of the breast or of the lining of the womb (mammary or endometrial carcinoma) or any other form of cancer, or have you ever had either of these conditions
 - abnormal bleeding from your vagina of unknown cause
 - certain types of jaundice (Dubin-Johnson or Rotor syndromes)
 - severe diabetes with changes to the blood vessels
 - liver tumours or if you have ever had these
 - any other long or short term liver disease
 - allergy to any of the ingredients of Co-Cyprindiol 2000/35 Coated Tablets

Do not take this medicine if you have had any of these conditions when you were pregnant:

- itching of your whole body (pruritus of pregnancy)
- the rash known as herpes gestationis
- worsening of inherited deafness (otosclerosis)
- yellowing of the skin (jaundice).

Important information about some of the ingredients of Co-Cyprindiol Tablets

Your medicine contains small quantities of inactive ingredients called lactose monohydrate and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

What special precautions should I take?

Before you start taking Co-Cyprindiol Tablets, your doctor should ask you about your medical history and also about other members of your family. Your doctor should ask you these questions on a regular basis, for example, when you come back to see your doctor for more pills. Your doctor will take your blood pressure and may check your breasts, abdomen and pelvic organs. You may need to have a cervical smear test and your doctor will also want to make sure you are not pregnant.

If anyone in your family has had any illness caused by blood clots, a heart attack, or a stroke at a young age, tell your doctor.

Inform your doctor if you develop any of the following conditions while you are taking Co-Cyprindiol 2000/35 Coated Tablets:

- severe depressive states, past or present
- varicose veins
- diabetes (diabetes mellitus) or a tendency towards diabetes

- high blood pressure (hypertension)
 - fits (epilepsy)
 - the inherited form of deafness known as otosclerosis
 - the disease of the nervous system called multiple sclerosis
 - the inherited disease called porphyria
 - calcium deficiency with cramps (tetany)
 - the movement disorder called Sydenham's chorea
 - breast problems, past or present
 - diseases of the heart and blood vessels (cardiovascular diseases).
 - kidney diseases
 - disturbed liver function
 - you are overweight (obese)
 - an intolerance to contact lenses
 - inflammation of connective tissue (systemic lupus erythematosus - SLE)
 - asthma
 - benign tumour of the womb (uterine fibroids)
 - gallstones
 - migraine
 - brown patches on the face and body (chloasma)
 - any disease that is prone to worsen during pregnancy.
- or, if:
- you have had inflamed veins (phlebitis)
 - anyone in your family has had breast cancer
 - anyone in your family has had any illness caused by blood clots, or a heart attack or stroke at a young age.

If any of these conditions gets worse or you have them for the first time this may be a sign that you should stop taking this medicine. When you stop taking this medicine it may take some time for your regular periods to return.

Ultraviolet (sunray) lamps or sunbeds and prolonged sunbathing should be avoided if you are taking Co-Cyprindiol 2000/35 Coated Tablets as this can increase the chance of a patchy discoloration of the skin called chloasma.

Stomach upsets

Being sick or having very bad diarrhoea may stop this medicine from working properly. If this happens and you are relying on this medicine for contraception, carry on taking it as usual, and also use another method of contraception (condoms or cap plus spermicide), until 7 days after you have recovered from the stomach upset. If you finish your pack before these 7 days, start the next pack the next day without a break. If you run two packs together you may not have a period until the end of two packs, but this is not harmful. If you do not have a period after the second pack, you must talk to your doctor before starting the next pack. If your stomach upset continues for some time, consult your doctor who may consider another form of contraception.

Should I stop taking Co-Cyprindiol 2000/35 Coated Tablets for any reason?

If you need to stop taking Co-Cyprindiol 2000/35 Coated Tablets, you should use another method of contraception such as a condom. You should stop taking your medicine and contact your doctor immediately if you experience any of the following:

- migraine for the first time, or if existing migraine occurs more often than usual
- unusually bad headaches or if you have headaches more often than before
- sudden changes to your eyesight, hearing, speech, sense of smell, taste or touch
- dizziness or fainting
- unusual pains in your leg or unusual swelling of your arms or legs, sharp pains in your chest or sudden shortness of breath, crushing pains or feelings of heaviness in your chest, coughing for no apparent reason or if one side of your body suddenly becomes very weak or numb. These may be symptoms of blood clot formation or symptoms of an inflammation of veins combined with the formation of blood clots (thrombophlebitis)
- your skin becomes yellow (jaundice), you develop hepatitis (inflammation of the liver) or if your whole body starts itching

- an increase in the number of fits (epileptic seizures)
- a large increase in your blood pressure
- severe depression
- severe upper abdominal pains or unusual swelling of your abdomen
- definite worsening of conditions when compared to similar conditions experienced during a previous pregnancy or whilst taking the pill in the past
- pregnancy
- surgery or immobilisation. You must stop Co-Cyprindiol 2000/35 Coated Tablets six weeks before a planned major operation (e.g. stomach surgery), if you are having any surgery to the legs, or medical treatment for varicose veins. Also if you are immobilised for a long time (e.g. you are in bed after an accident or operation or you have a plaster cast on a broken leg). Your doctor will advise you when to start taking Co-Cyprindiol 2000/35 Coated Tablets again.

Can I take other medicines with Co-Cyprindiol 2000/35 Coated Tablets?

Some medicines may stop Co-Cyprindiol 2000/35 Coated Tablets working properly as a contraceptive. If you are taking any other medicine while you are relying on Co-Cyprindiol 2000/35 Coated Tablets for contraception, be sure to tell your doctor (or dentist). Your doctor (or dentist) can tell you whether you should use extra contraceptive precautions and for how long.

Medicines which can sometimes stop Co-Cyprindiol 2000/35 Coated Tablets from working properly are:

- antibiotics (such as ampicillin and rifampicin);
- griseofulvin (which is used to treat fungal infections)
- phenylbutazone (which is used as an anti-inflammatory drug to treat some types of joint diseases)
- phenytoin, primidone, phenobarbital and some other medicines used in people with epilepsy
- carbamazepine (which can be used to treat epilepsy or other illnesses).

Inform your doctor if you are relying on Co-Cyprindiol 2000/35 Coated Tablets for contraception and you are taking any of these medicines, you will need to use an extra contraceptive method (condoms or cap plus spermicide) while you are taking the other medicine and for 7 days (4 weeks in the case of rifampicin) after you stop taking it. If your present pack ends before these 7 days, start the next pack the next day without a break. If you run two packs together you may not have a period until the end of two packs, but this is not harmful. If you do not have a period after the second pack, you must talk to your doctor before you start the next pack.

Medicines applied to the skin, including antibiotics, will not affect the contraceptive reliability of Co-Cyprindiol 2000/35 Coated Tablets. If you are diabetic your doctor may alter the dose of medicine required to treat your diabetes.

The herbal remedy St John's Wort (*Hypericum perforatum*) should not be taken at the same time as Co-Cyprindiol 2000/35 Coated Tablets. If you are in any doubt, check with your doctor or pharmacist.

3. How to take Co-Cyprindiol 2000/35 Coated Tablets

If you are relying on this medicine for contraception, it is important that you follow these instructions carefully.

When to start

- If you are new to Co-Cyprindiol 2000/35 Coated Tablets or are starting it again after a break, take your first tablet on the first day of bleeding of your next period. For other users, follow instructions for "Changing from another type of oral contraceptive", "Starting Co-Cyprindiol Tablets after having a baby" or "Starting Co-Cyprindiol Tablets after a miscarriage or an abortion".
- Start with a pill marked with the correct day of the week. For

instance, if your period starts on a Wednesday, start with a pill marked "Wed".

Taking your first pack of Co-Cyprindiol 2000/35 Coated Tablets

- After taking your first pill, take one pill each day, following the directions of the arrows, until you have finished all 21 pills in the pack.
- You should try to take the pill at the same time every day, for example, after breakfast. Swallow each pill whole, with water if necessary.
- By starting in this way you will have contraceptive protection at once.

Your seven pill-free days

After you have taken all 21 tablets, you have 7 days when you take no tablets. A few days after you have taken the last pill from each pack, you will have a period. Your periods will be regular, probably lighter than before and almost always painless. The feelings that often make the last days before a period unpleasant (called pre-menstrual syndrome) usually disappear. You are very unlikely to become pregnant during the 7 day break from taking the pill, as long as you have taken your pills correctly, and start the next pack on time.

Taking your next pack of Co-Cyprindiol 2000/35 Coated Tablets

Start taking your next pack of Co-Cyprindiol 2000/35 Coated Tablets after 7 pill-free days even if you are still bleeding. Each new pack will begin on the same day of the week as the one before.

Changing from another type of oral contraceptive

If you follow the instructions given below you will have contraceptive protection at once

21 day pill

If you are taking a 21 day contraceptive pill, finish that pack and then start taking Co-Cyprindiol 2000/35 Coated Tablets the next day. Do not leave a gap between packs. Start with a pill marked with the correct day of the week. Then follow the instructions as described before. (see "Taking your first pack of Co-Cyprindiol 2000/35 Coated Tablets"). You may not have a period until the end of the first Co-Cyprindiol 2000/35 Coated Tablets pack or you may have some bleeding on pill-taking days, but do not worry.

Every Day (ED) combined pill (28 day pill)

Co-Cyprindiol 2000/35 Coated Tablets should be started the day after taking the last active tablet from the Every Day pill pack. If you are not sure which tablets are the active ones, ask your doctor or pharmacist.

Start with a pill marked with the correct day of the week. Return any remaining inactive tablets from your old Every Day pack to your pharmacist. Then follow the instructions as before (see "Taking your first pack of Co-Cyprindiol 2000/35 Coated Tablets "). You may not have a period until the end of the first Co-Cyprindiol 2000/35 Coated Tablets pack or you may have some bleeding on pill-taking days, but do not worry.

Mini pill (progestogen-only pill)

The first Co-Cyprindiol 2000/35 Coated Tablets should be taken on the first day of the period, even if you have already taken a mini pill on that day. Return any mini pills left in your old pack to your pharmacist. Start with a pill marked with the correct day of the week and follow the instructions as before (see "Taking your first pack of Co-Cyprindiol 2000/35 Coated Tablets ").

Starting Co-Cyprindiol 2000/35 Coated Tablets after having a baby

If you have just had a baby, your doctor may advise you to start taking Co-Cyprindiol 2000/35 Coated Tablets 21 days after delivery. You do not have to wait for a period. You will need to use another method of contraception until you start Co-Cyprindiol 2000/35 Coated Tablets and for the first 7 days of pill taking. Follow the instructions as before (see "Taking your first pack of Co-Cyprindiol 2000/35 Coated Tablets "). You must not breastfeed if you take Co-Cyprindiol 2000/35 Coated Tablets.

Starting Co-Cyprindiol 2000/35 Coated Tablets after a miscarriage or an abortion

If you have just had a miscarriage or an abortion your doctor may advise you to start using Co-Cyprindiol 2000/35 Coated Tablets immediately. Follow the instructions as before (see "Taking your first pack of Co-Cyprindiol 2000/35 Coated Tablets ").

When can I expect to see improvement in my skin?

Unlike treatments that are rubbed on the skin, this treatment does not so much attack existing spots as reduce the formation of new spots. It does this by working at the point at which the androgens stimulate the grease-glands to produce too much grease. The first thing that you will notice is that your skin has become much less greasy. This should be obvious in the first few weeks. After about three months you should see a definite improvement in acne. If you are taking this medicine to treat excessive hair growth on your body or face, you may have to wait a few months, possibly longer, to see a definite improvement.

How long can I take Co-Cyprindiol 2000/35 Coated Tablets?

Your doctor may stop treating you with this medicine when your skin is completely clear, or the amount of body and facial hair growth has decreased. You will be able to have further courses of treatment if the problem returns.

What do I do if I miss a period?

If you have no bleeding in the 7 day break, whether you have missed tablets or not, tell your doctor as soon as possible and do not start another pack until your doctor tells you to. In the meantime, you should use other forms of contraception such as condoms or a cap plus spermicide.

What if I have bleeding between periods?

A small number of women may have a breakthrough bleeding or spotting while taking this medicine, especially during the first few months. Normally, this will stop in a day or two. Keep taking the pills as usual, and the problem should disappear after the first few packs. If the bleeding keeps returning or is long lasting, talk to your doctor. Also, if you start to have breakthrough bleeding after being on this medicine for a long time, you should see your doctor. Unexpected bleeding may also be a sign of irregular pill-taking, so try to take your pill at the same time every day.

What should I do if I forget to take a pill and am relying on Co-Cyprindiol 2000/35 Coated Tablets for contraceptive cover?

1. *If you are more than 12 hours late in taking a pill, or have missed more than one pill*

Contraceptive protection may be lower, so you must use extra protection. Follow the instructions for the 7-day rule.

7-day rule

- take the most recent 'late' pill and continue to take your next pills at your normal times **and**
- use an extra contraceptive method (condoms or cap plus spermicide) for the next 7 days **and**
- if your present pack ends before the 7 days do, start the next pack the next day, without a break. This means taking a pill every day during your normal 7 pill-free days. You will not have a period until you have finished the next pack, but this is not harmful. You may see some bleeding on pill-taking days, but do not worry. If no bleeding occurs in the 7-day break see the section entitled "What do I do if I miss a period".

2. *If one pill is 12 hours late or less*

Don't worry. Contraceptive protection should not be affected if you take the late pill at once, and keep taking your next pills at the usual time.

What should I do if I lose a pill?

If you lose a pill, the easiest thing to do is to take the last pill of the pack in place of the lost pill. Then take all the pills on their proper days. Your cycle will be one day shorter than normal, but

contraceptive protection will not be affected. After your 7 pill-free days you will have a new starting-day, one day earlier than before. Should you lose a pack of pills halfway through, ask your doctor or pharmacist what to do.

What if I want to have a baby?

The bleeding you have after each pack (including the last pack) is not a true period. Your doctor relies on the date of your last true period before you get pregnant to tell you when your baby will be born. So, if you stop taking Co-Cyprindiol 2000/35 Coated Tablets to have a baby, use another method of contraception until you have had a true period. However, it will not be harmful if you become pregnant straight away.

What if I take too many tablets?

Overdosage may cause nausea, vomiting and, in females, withdrawal bleeding. You should consult your doctor who will be able to advise you what action is necessary.

4. Possible side effects

As with all medicines Co-Cyprindiol 2000/35 Coated Tablets can have side effects. These can be mild or serious.

Mild reactions

Mild unwanted effects can occur in the first few months after starting Co-Cyprindiol 2000/35 Coated Tablets.

- bleeding and spotting between your periods for the first few months but this usually stops once your body has adjusted to Co-Cyprindiol 2000/35 Coated Tablets. If it continues, becomes heavy or starts again, contact your doctor
- headaches
- feeling sick, being sick and stomach upsets
- sore breasts
- depressive moods, loss of interest in sex
- changes in weight
- yellow brown patches on the skin (chloasma). This may happen even if you have been using Co-Cyprindiol 2000/35 Coated Tablets for a number of months and may be reduced by avoiding too much sunlight
- poor tolerance to contact lenses.

If you think you have an unwanted effect due to Co-Cyprindiol 2000/35 Coated Tablets, even if it is not included in this leaflet, tell your doctor or a pharmacist about it.

Serious reactions

More serious reactions have sometimes been associated with contraceptive pills that contain oestrogen and progestogen, e.g. thrombosis (the formation of a clot in blood vessels) or liver disease. These are explained more fully in the "Should I stop taking Co-Cyprindiol 2000/35 Coated Tablets for any reason?" section above.

If you think that you have a serious reaction to Co-Cyprindiol Tablets, stop taking your tablets and consult your doctor immediately.

Withdrawal effects

You may experience infrequent or absence of periods after stopping Co-Cyprindiol 2000/35 Coated Tablets, especially if you had these conditions before you started using this medicine.

Effect on blood tests

The use of this medicine may affect the results of certain laboratory tests. Always tell your doctor or the laboratory staff that you are using Co-Cyprindiol 2000/35 Coated Tablets.

5. Storing Co-Cyprindiol 2000/35 Coated Tablets

Store in the original package.

Store all medicines out of the sight and reach of children.

The expiry date is printed on the pack and on each blister strip. Do not use after this date. Return any unused tablets to your pharmacist for safe disposal.

Date of last revision of this leaflet: April 2006

Further information

This leaflet does not contain all the information about this medicine.

If you have any questions or are not sure about anything, ask your doctor or pharmacist.

**CO-CYPRINDIOL 2000/35 COATED TABLETS
PL 14894/0413**

LABELLING

(SUN) → (MON) → (TUE) → (WED) → (THU) → (FRI) → (SAT)

RANBAXY Co-Cyprindiol 2000/35 Coated Tablets **POM**
Ranbaxy (UK) Ltd PL No.: 14894/0413

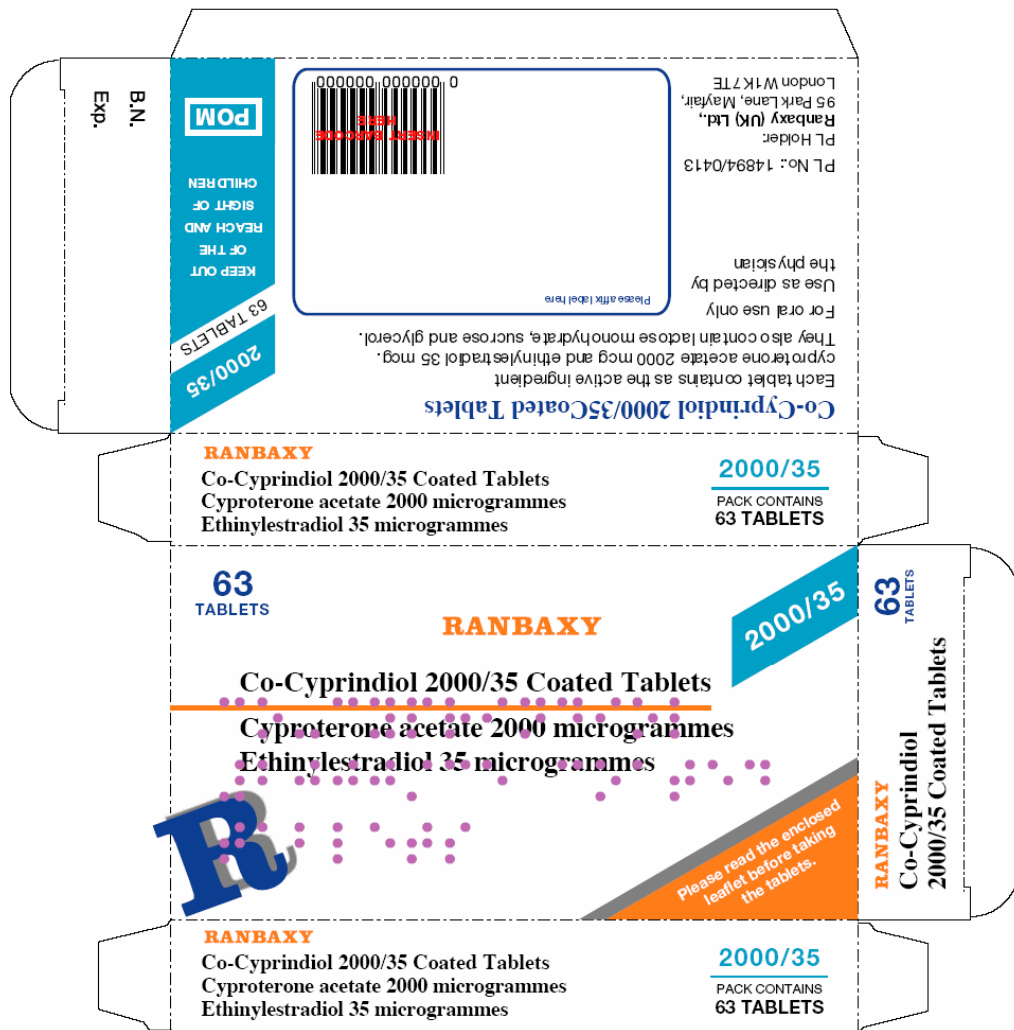
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RANBAXY Co-Cyprindiol 2000/35 Coated Tablets **POM**
Ranbaxy (UK) Ltd PL No.: 14894/0413

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Braille translation is

co-cyprindiol
 2000/35 coated
 tablets

