CO-CYPRINDIOL 2000/35 TABLETS
(cyproterone acetate and ethinylestradiol)
PL 36390/0027
UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted STD Chemicals Limited a Marketing Authorisation (licence) for the medicinal product Co-cyprindiol 2000/35 Tablets (PL 36390/0027) on 06 March 2012. This is a prescription-only medicine (POM) used in women for the treatment of:

- severe acne that has not improved after long-term use of oral antibiotics
- excessive hair growth on the face and body (hirsutism).

This medicine is prescribed as a treatment for the skin. Although Co-cyprindiol 2000/35 Tablets are used for treating acne and hirsutism, this medicine is also an effective oral contraceptive (‘the Pill’).

Co-cyprindiol 2000/35 Tablets contain the active substances, cyproterone acetate and ethinylestradiol. Cyproterone acetate is an anti-androgen and ethinylestradiol is an estrogen.

In women, in addition to making female sex hormones, the body also makes male sex hormones (androgens). Androgens cause the grease-glands in the skin to make large amounts of an oily substance called sebum. If the body produces too many androgens, or if the skin is especially sensitive to the effects of androgens, too much sebum may be produced by these grease-glands, which can then cause acne when blocked grease-glands become infected and inflamed.

One of the active substances in Co-cyprindiol 2000/35 Tablets, cyproterone acetate, works by blocking the effects of androgens produced by the body. The medicine will also reduce the activity of the ovaries so that they produce only small amounts of hormones, including androgens.

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 Tablets outweigh the risks and a Marketing Authorisation was granted.
CO-CYPRIINDIOL 2000/35 TABLETS
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PL 36390/0027

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Marketing Authorisation for the medicinal product Co-cyprindiol 2000/35 Tablets (PL 36390/0027) to STD Chemicals Limited on 06 March 2012. The product is available as a prescription only medicine (POM) recommended for use in women only for the treatment of:

• severe acne, refractory to prolonged oral antibiotic therapy
• moderately severe hirsutism.

Although Co-cyprindiol 2000/35 Tablets also act as an oral contraceptive, the tablets should not be used in women solely for contraception, but should be reserved for those women requiring treatment for the androgen-dependent skin conditions described.

The application was submitted as an abridged application according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Co-cyprindiol 2000/35 Tablets (PL 08137/0081), which was originally granted a Marketing Authorisation to Neolab Limited on 26 June 2003.

Co-cyprindiol 2000/35 Tablets contain two active substances, cyproterone acetate and ethylhexadiol).

When used in combination, cyproterone acetate and ethylhexadiol block androgen-receptors and reduce 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 Tablets also act as an oral contraceptive, the tablets are not recommended in women solely for contraception, but should be reserved for those women requiring treatment for the androgen-dependent skin conditions described.

No new data were submitted nor were they necessary for this simple application, as the data are identical to those of the previously granted cross-reference product.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 36390/0027
PROPRIETARY NAME: Co-cyprindiol 2000/35 Tablets
ACTIVE(S): Cyproterone acetate and ethinylestradiol
COMPANY NAME: STD Chemicals Limited
E.C. ARTICLE: Article 10c of Directive 2001/83/EC
LEGAL STATUS: POM

1. INTRODUCTION
This is an abridged application for Co-cyprindiol 2000/35 Tablets (PL 36390/0027), submitted under Article 10c of Directive 2001/83/EC, as amended. The proposed Marketing Authorisation Holder is STD Chemicals Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.

The application cross-refers to Co-cyprindiol 2000/35 Tablets (PL 08137/0081), which was originally granted a Marketing Authorisation to Neolab Limited on 26 June 2003.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The proposed name of the product is Co-cyprindiol 2000/35 Tablets (PL 36390/0027). The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
Each tablet contains 2 milligrams of cyproterone acetate and 35 micrograms of ethinylestradiol. The tablets are for oral use and are packaged in polyvinyl chloride/aluminium blisters. These are packed into cardboard cartons with Patient Information Leaflets, in pack sizes of 21 and 63 tablets (21 tablets per blister).

The proposed shelf-life (36 months) and storage conditions (‘Do not store above 25°C. Store in the original package.’) are consistent with the details registered for the cross-reference product.

2.3 Legal status
On approval, the product will be available as a prescription-only medicine (POM).

2.4 Marketing Authorisation Holder/Contact Persons/Company
STD Chemicals Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, United Kingdom

The Qualified Person (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 Good Manufacturing Practice (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
With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

2.11 Bioequivalence
No bioequivalence data are required to support this informed consent application, as the proposed product is manufactured to the same formula and utilising the same process as the reference product Co-cyprindiol 2000/35 Tablets (PL 08137/0081).

3. EXPERT REPORTS
The applicant cross-refers to the data for Co-cyprindiol 2000/35 Tablets (PL 08137/0081), to which it claims to be identical. This is acceptable.

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 (SmPC)
The proposed Summary of Product Characteristics is consistent with the details registered for the cross-reference product.
6. PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

PIL
The approved PIL is satisfactory and in line with the approved SmPC. It is consistent with the details registered for the cross-reference product.

Neolab Limited has previously submitted results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, for the reference product Co-cyprindiol 2000/35 Tablets (PL 08137/0081). The results indicate that the leaflet is well-structured and organised, easy to understand, and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

As the leaflet for Co-cyprindiol 2000/35 Tablets (PL 08137/0081) and this product are considered the same, no further user testing of the leaflet for this product is necessary.

Carton and blister label
The proposed artwork is consistent with 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. CONCLUSION
The data submitted with the application are acceptable. The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As the application is for an identical version of an already authorised product, it is not expected that environmental exposure will increase following approval of the marketing authorisation for the proposed product.

The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has not submitted a Risk Management Plan (RMP). As the application is for an identical version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active ingredient is well-established.

The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

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

NON-CLINICAL
No new non-clinical data were and submitted none are required for an application of this type.

EFFICACY
This application is identical to a previously granted application for Co-cyprindiol 2000/35 Tablets (PL 08137/0081). No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with cyproterone acetate and ethinylestradiol is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.
CO-CYPRINDIOL 2000/35 TABLETS
(cyproterone acetate and ethinylestradiol)
PL 36390/0027

**STEPS TAKEN FOR ASSESSMENT**

1. The MHRA received the Marketing Authorisation application on 08 April 2011.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 27 April 2011.
3. Following assessment of the application, the MHRA requested further information relating to the dossier on 06 July 2011 and 15 September 2011.
4. The applicant responded to the MHRA’s request, providing further information on 11 August 2011 and 31 January 2012.
4. The application was granted on 06 March 2012.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Co-cyprindiol 2000/35 Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Cyproterone acetate 2 milligrams and ethinylestradiol 35 micrograms.
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Yellow, round biconvex tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Co-cyprindiol is recommended for use in women only for the treatment of (a) severe acne, refractory to prolonged oral antibiotic therapy; (b) moderately severe hirsutism.

Although co-cyprindiol also acts as an oral contraceptive, it should not be used in women solely for contraception, but should be reserved for those 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. Patients who are using co-cyprindiol should not therefore use an additional hormonal contraceptive, 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).

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

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, 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):
Co-cyprindiol should be started after taking the last active tablet from the Every Day Pill pack. The first co-cyprindiol tablet is taken the next day. Additional contraceptive precautions are 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.

**Post-partum and post-abortum use:**
After pregnancy, co-cyprindiol can be started 21 days after a vaginal delivery, provided that 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 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 contra-indicated with co-cyprindiol. After a first-trimester abortion, co-cyprindiol may be started immediately in which case 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, and 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. Additionally, therefore, 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. 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 the tablet-free interval following the end of the second pack, 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 thrombo-embolism (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. The presence of a severe of multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see section 4.4.).
7. Sickle-cell anaemia.
8. Mammary or endometrial carcinoma, or a history of these conditions.
9. Severe diabetes mellitus with vascular changes.
10. Disorders of lipid metabolism.
11. History of herpes gestationis.
13. Undiagnosed abnormal vaginal bleeding.
14. Hypersensitivity to any of the components of Co-cyprindiol Tablets.
4.4 Special warnings and precautions for use

Warnings:
Like many other steroids, co-cyprindiol, 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 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 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, and must be excluded before such treatment is begun.

Co-cyprindiol 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 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 immediately”).

There is some epidemiological evidence that the incidence of VTE is higher in users of co-cyprindiol when compared to users of COCs with low oestrogen content (<50µg).

The user group of co-cyprindiol 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).

**Estimated cumulative numbers of breast cancers per 10,000 women diagnosed in 5 years of use and up to 10 years after stopping COCs, compared with numbers of breast cancers diagnosed in 10,000 women who had never used COCs**

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 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 very 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 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, 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.

Patients with a history of depression or any condition mentioned above should be monitored during treatment with co-cyprindiol.

If co-cyprindiol is discontinued, other methods of contraception should be introduced if needed.

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, especially when these conditions existed prior to use. Women should be informed of this possibility.
### 4.5 Interaction with other medicinal products and other forms of interaction

Hepatic enzyme inducers such as barbiturates, primidone, phenobarbitone, phenytoin, phenylbutazone, rifampicin, carbamazepine and griseofulvin can impair the contraceptive efficacy of co-cyprindiol. 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, possibly by altering the intestinal flora.

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, although it has not been shown. 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 Fertility, Pregnancy and lactation

Contra-indicated.

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 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, and must be excluded before such treatment is begun.

### 4.7 Effects on ability to drive and use machines

None known.

### 4.8 Undesirable effects

There is an increased risk of venous thromboembolism for all women who use Co-cyprindiol 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, depressive moods can occur.

Post-marketing reports of severe depression in patients using co-cyprindiol have been received. However, a causal relationship between clinical depression and co-cyprindiol has not been established.

In predisposed women, use of co-cyprindiol can sometimes cause chloasma 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 it is to be expected in some patients. Indeed, it may be beneficial where heavy periods were previously experienced.

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.

Intermenstrual bleeding:
“Spotting” or heavier “breakthrough bleeding” sometimes occur during tablet taking, especially in the first few cycles, and normally cease spontaneously. Co-cyprindiol should therefore, 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 in the case of spotting which occurs at regular intervals in several consecutive cycles or which occurs for the first time after long use of co-cyprindiol.

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.

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 blocks androgen-receptors. It also reduces androgen synthesis both by negative feedback effect on the hypothalamo-pituitary-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 in a wide dose range. The ingestion of Co-cyprindiol 2000/35 Tablets effects 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 15β-hydroxy derivative.
Some dose parts are excreted unchanged with the bile fluid. Most of the dose is excreted in 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. 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 from Co-cyprindiol was 109% when compared to an aqueous microcrystalline suspension.

**Ethinylestradiol:**
Orally administered ethinylestradiol is rapidly and completely absorbed. Following ingestion of Co-cyprindiol 2000/35 Tablets 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. 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. During treatment with co-cyprindiol SHBG concentrations in serum increased from about 100nmol/l to 300nmol/l and the serum concentrations of CBG were increased from about 50μg/ml to 95μg/ml.

**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
Purified talc
Magnesium stearate
Hypromellose
Propylene glycol
Titanium dioxide (E171)
Quinoline yellow (E104)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container
PVC/aluminium blister strips containing 21 tablets. Each carton contains either 1 or 3 blister strip packs.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0027

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/03/2012

10 DATE OF REVISION OF THE TEXT
06/03/2012
PATIENT INFORMATION LEAFLET

Co-ndiprol 200/35 Tablets (PL 36390/0027) - 21 -

PATIENT INFORMATION LEAFLET

1. WHAT CO-NDIPROL TABLETS ARE AND WHAT THEY ARE USED FOR

Co-ndiprol Tablets contain a combination of 2 active substances, ethinylestradiol (an estrogen) and norethisterone (a progestogen). This medicine is used mainly for the treatment of women in whom one or more of the following symptoms may occur:

- Unwanted bleeding
- Heavy periods

1. WHAT CO-NDIPROL TABLETS ARE AND WHAT THEY ARE USED FOR

Co-ndiprol Tablets are usually taken on the first day of a bleed.
The newfound Mr. John’s work (apricot permutal) showed to be not for the same time as Co-cyprindol tablets. If you already take a Mr. John’s supplement, also this it and start taking this Co-cyprindol tablet immediately.

In some cases, this medicine may affect other medicines you are taking. These may increase or decrease the amount of Co-cyprindol tablets in your body. Use this medicine only under your doctor’s or pharmacist’s care.

You should bring your Co-cyprindol tablets with you to your doctor or pharmacist. Otherwise, your pharmacist will also work out the treatment for you and this Co-cyprindol tablets is being used.

When to start

- If you have been taking Co-cyprindol Tablets before you start taking this medicine, you should carefully read the instructions for use.
- Start with a small amount of this medicine and slowly increase your daily dose over time until the right dose is reached.

Taking any other tablet or Co-cyprindol Tablets

- Do not drive a car or operate machinery until you know how Co-cyprindol Tablets affect you.
- If you feel dizzy or light-headed, sit or lie down.

Depending on the effect of this medicine, you may have to stop taking it and start taking another Co-cyprindol Tablets instead.

The last Co-cyprindol Tablets should be taken on the first day of the period. Even if you have already taken the first tablet, this should be continued until menstruation ends.

You must stop taking Co-cyprindol Tablets before starting this medicine and start taking Co-cyprindol Tablets at the lowest dose possible.

What to do if you think you have missed a dose

- If you forget to take Co-cyprindol Tablets, take it as soon as you remember. However, if you are late, you must stop taking Co-cyprindol Tablets and start taking another Co-cyprindol Tablets.

What if you have any unusual bleeding

- If you have excessive bleeding or vaginal bleeding that is not regular, you should stop taking Co-cyprindol Tablets and contact your doctor immediately.

How long to use

- Your doctor will decide the length of time you need to use this medicine. Typically, this medicine is used for 2-3 months.

What if you are having unusual bleeding

- If you have spotting or breakthrough bleeding, you may need to start taking Co-cyprindol Tablets at a different dose or use a different contraceptive method.

How to stop using this medicine

- If you want to stop using Co-cyprindol Tablets, you should talk to your doctor about the best way to do this.

Side effects

- Common side effects of Co-cyprindol Tablets include:
  - nausea
  - vomiting
  - irregular menstrual bleeding

- Less common side effects of Co-cyprindol Tablets include:
  - increased uterine bleeding
  - breast tenderness

- Rare side effects of Co-cyprindol Tablets include:
  - blood clots
  - liver problems

- Severe side effects of Co-cyprindol Tablets include:
  - allergic reactions
  - liver failure

- If you experience any of these serious side effects, stop taking Co-cyprindol Tablets and seek medical attention immediately.

Interactions

- Do not take Co-cyprindol Tablets if you are taking any other medicine that could interact with it.
- Tell your doctor or pharmacist about all medicines you are taking.

Other information

- This medicine is not recommended for use in women who are breastfeeding.
- Co-cyprindol Tablets should not be used by women who have had a stroke or heart attack.

Important note about the next Co-cyprindol Tablets

- You may need to take the next Co-cyprindol Tablets at a different time if you are planning to breastfeed.
- If you are planning to breastfeed, you may need to stop taking Co-cyprindol Tablets.

You should tell your doctor or pharmacist if you are taking any other medicine or if you are pregnant or breastfeeding.

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Importan
Co-Cyprindiol 2000/35 Tablets

Each film-coated tablet contains Cyproterone Acetate 20 mg and Ethinylestradiol 35 micrograms.

Distributor:
Parniga UK Ltd, 57 High Street,
Odessa, Herts, RO29 1LT.
PL.369/0027
PL Holder: STD Chemicals Ltd.
Hillbrow house, Hillbrow Road,
Esher, Surrey, KT10 9XW.

Co-Cyprindiol 2000/35 Tablets