Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cyproterone Acetate/Ethinylestradiol Tablets 2mg/0.035mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One coated tablet contains:

Cyproterone acetate 2.000 mg
Ethinylestradiol 0.035 mg

and also contains 31.115 mg of Lactose Monohydrate and 19.371 mg of Sucrose
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated Tablet.

Each tablet is round, beige in colour with no markings.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cyproterone Acetate/ Ethinylestradiol Tablets 2mg/0.035mg is recommended for use in women only for the treatment of:
- severe acne, refractory to prolonged antibiotic therapy or
- moderately severe hirsutism.

Although Cyproterone Acetate/Ethinylestradiol 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 Cyproterone Acetate/Ethinylestradiol 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 conditions described.

4.2 Posology and method of administration

Cypterone Acetate/Ethinylestradiol inhibits ovulation and thereby prevents conception. Patients who are using Cyproterone Acetate/Ethinylestradiol 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 Cyproterone Acetate/Ethinylestradiol 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 Cyproterone Acetate/Ethinylestradiol, follow the instructions given below:

Changing from 21-day combined oral contraceptives: The first tablet of Cyproterone Acetate/Ethinylestradiol 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):
Cyproterone Acetate/Ethinylestradiol should be started after taking the last active tablet from the Every Day Pill pack. The first Cyproterone Acetate/Ethinylestradiol tablet is taken the next day. Additional contraceptive precautions are not then required.

Changing from a progestogen-only pill (POP):
The first tablet of Cyproterone Acetate/Ethinylestradiol 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, Cyproterone Acetate/Ethinylestradiol 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 Cyproterone Acetate/Ethinylestradiol. After a first-trimester abortion, Cyproterone Acetate/Ethinylestradiol may be started immediately in which case no additional contraceptive precautions are required.

Length of use
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 Cyproterone Acetate/Ethinylestradiol is not continued solely to provide oral contraception. Repeat courses of Cyproterone Acetate/Ethinylestradiol may be given if the androgen-dependent condition(s) recur.

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

Preparations containing oestrogen/progestogen combinations should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during their use, the product should be stopped immediately.

• Existing or a history of confirmed venous thromboembolism (VTE) (e.g deep venous thrombosis, pulmonary embolism), major surgery with prolonged immobilisation

• Existing or previous arterial thrombotic or embolic processes (stroke (e.g. transientischaemic attack, ischemic stroke, haemorrhagic stroke), angina, myocardial infarction).

• Conditions which predispose to thromboembolism e.g. disorders of the clotting processes, valvular heart disease and atrial fibrillation, known thrombogenic mutations

• Severe and/or multiple risk factor(s) for venous or arterial thrombosis (see section 4.4)

• Severe or uncontrolled hypertension or hypertension associated with vascular disease

• History of migraine with focal neurological symptoms.

• Severe diabetes mellitus with vascular changes.

• Presence or history of severe hepatic disease e.g. active viral hepatitis and severe cirrhosis, as long as liver function values have not returned to normal.

• Presence or history of liver tumours (benign or malignant).

• Current or history of breast cancer

• Known or suspected pregnancy (see section 4.6)

• Breast-feeding (see section 4.6).

• Hypersensitivity to the active substances or to any of the excipients.

Relevant UK clinical guidance on COCs should also be consulted.

Cyproterone Acetate/Ethinylestradiol is not for use in men.

4.4 Special warnings and precautions for use

Medical Examination

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.

Exclude the likelihood of pregnancy before starting treatment.

Undiagnosed vaginal bleeding that is suspicious for underlying conditions should be investigated.

Warnings:
Women should be advised that Cyproterone Acetate/Ethinylestradiol does not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Conditions which require strict medical supervision

The decision to prescribe Cyproterone Acetate/Ethinylestradiol must be made using clinical judgement and in consultation with the woman. Deterioration or first appearance of any of these conditions may indicate that Cyproterone Acetate/Ethinylestradiol should be discontinued:

• Diabetes mellitus, with mild vascular disease or mild nephropathy, retinopathy or neuropathy
• Hypertension that is adequately controlled, i.e. systolic >140 to159 mm Hg or diastolic > 90 to 94mmHg (see also Section 4.4 'Reasons for stopping Cyproterone Acetate/Ethinylestradiol immediately'
• porphyria
• clinical depression
• obesity
• migraine
• cardiovascular diseases
• chloasma

Patients with a history of depression or any condition mentioned above should be monitored during treatment with Cyproterone Acetate/Ethinylestradiol .

Reasons for stopping Cyproterone Acetate/Ethinylestradiol immediately:
When stopping oral contraception non-hormonal contraception should be used to ensure contraceptive protection is maintained, if needed.

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 thrombosis or blood clots (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. Significant rise in blood pressure
7. Onset of severe depression.
8. Severe upper abdominal pain or liver enlargement.
9. Clear worsening of conditions known to deteriorate during use of hormonal contraception or during pregnancy (see section 4.4 'Conditions which deteriorate in pregnancy or during previous COC use' under 'Other conditions'.
10. Pregnancy is a reason for stopping immediately (see section 4.6)

<u>Circulatory disorders</u>

• *<u>Venous thromboembolism</u>*
Cyproterone Acetate/Ethinylestradiol 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 Cyproterone Acetate/Ethinylestradiol 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.

There is some epidemiological evidence that the incidence of VTE is higher in users of Cyproterone Acetate/Ethinylestradiol when compared to users of COCs with low oestrogen content (< 50µg).

The risk of VTE increases with:
- age
- obesity (body mass index over 30 kg/m2)

- a personal or family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary or acquired predisposition is suspected, the woman should be referred to a specialist for advice before deciding about Cyproterone Acetate/Ethinylestradiol or any COC use (see section 4.4 for further information on biochemical factors under 'Other factors affecting circulatory events')
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC or Cyproterone Acetate/Ethinylestradiol use (in the case of elective surgery at least six weeks in advance) and not to resume until two weeks after complete remobilisation.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

The increased risk of thromboembolism in the puerperium must be considered when recommencing treatment (see section 4.2)

Common signs/symptoms of VTE include:
- severe pain in the calf of one leg; swelling of the lower leg
- sudden breathlessness, chest pain.

Arterial thromboembolic-related conditions
The use of a combined oral contraceptive or Cyproterone Acetate/Ethinylestradiol may also increase the risk of conditions such as stroke and myocardial infarction which are secondary to arterial thromboembolic events. Other risk factors for arterial thromboembolism include:
- age
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
- a positive family history (i.e., venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary or acquired predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC or Cyproterone Acetate/Ethinylestradiol use
- obesity (body mass index over 30 kg/m2)
- dyslipoproteinaemia
- hypertension
- valvular heart disease
- atrial fibrillation
- migraine. An increase in frequency or severity of migraine during COC or Cyproterone Acetate/Ethinylestradiol use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC or Cyproterone Acetate/Ethinylestradiol

Common signs/symptoms associated with arterial thromboembolism include:
- sudden severe pain in the chest, whether or not reaching to the left arm;
- any unusual severe, prolonged headache, especially if it occurs for the first time or gets progressively worse, or is associated with any of the following symptoms:
- sudden partial or complete loss of vision or diplopia;
- aphasia;
- vertigo;
- collapse with or without focal epilepsy;
- weakness or very marked numbness suddenly affecting one side or one part of the body.

Other factors affecting circulatory events

The user group of Cyproterone Acetate/Ethinylestradiol 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.

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

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with COC or Cyproterone Acetate/Ethinylestradiol use.

Tumours

Like many other steroids, Cyproterone Acetate/Ethinylestradiol , 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.

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 high dose combined oral contraceptives offer substantial protection against both ovarian and endometrial cancer. However, it is not clear whether low dose COCs or Cyproterone Acetate/Ethinylestradiol confer protective effects to the same level

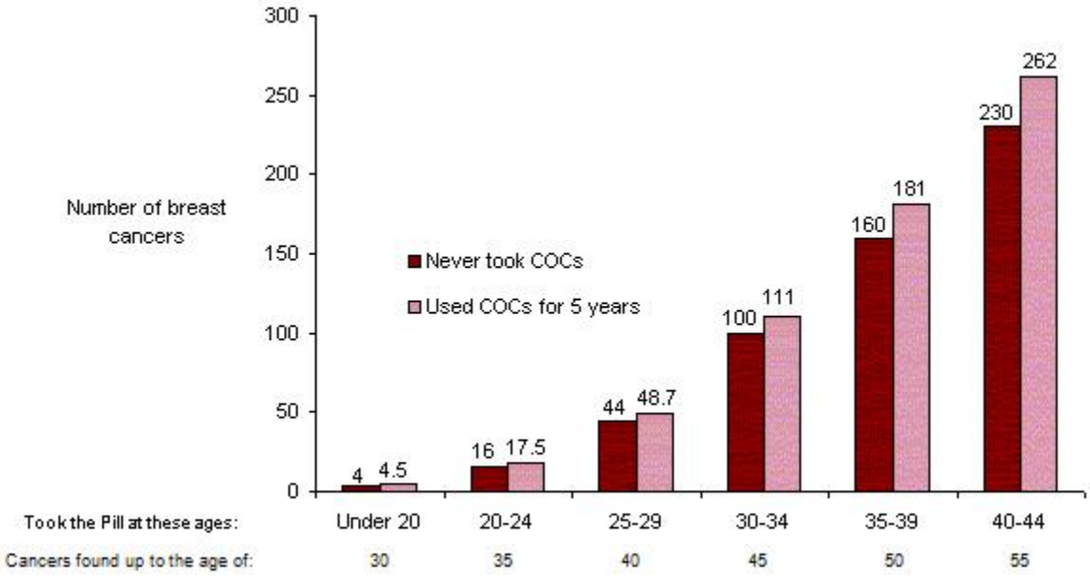
Breast cancer
A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COCs). The observed pattern of increased risk may be due to an earlier diagnosis 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 (see bar chart).

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



Cervical Cancer

The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g., cervical screening and sexual behaviour including use of barrier contraceptives.

Liver Cancer

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 Cyproterone Acetate/Ethinylestradiol . If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential diagnosis

Other conditions

The possibility cannot be ruled out that certain chronic diseases may occasionally deteriorate during the use of Cyproterone Acetate/Ethinylestradiol .

Known hyperlipidaemias

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

Women with hyperlipidaemias are at an increased risk of arterial disease (see section 4.4 'Circulatory disorders'). However routine screening of women on COCs or Cyproterone Acetate/Ethinylestradiol is not appropriate.

Blood pressure

Hypertension is a risk factor for stroke and myocardial infarction (see section 4.4 'Arterial thromboembolic-related conditions'). Although small increases in blood pressure have been reported in many women taking COCs or oestrogen/progestogen combinations like Cyproterone Acetate/Ethinylestradiol , clinically relevant increases are rare. However, if sustained hypertension develops during the use of Cyproterone Acetate/Ethinylestradiol , antihypertensive treatment should normally be instigated at a level of 160/100 mm Hg in uncomplicated patients or at 140/90 mm Hg in those with target organ damage, established cardiovascular disease, diabetes or with increased cardiovascular risk factors. Decisions about the continued use of Cyproterone Acetate/Ethinylestradiol , should be made at lower BP levels, and alternative contraception may be advised.

Conditions which deteriorate with pregnancy or during previous COC or Cyproterone Acetate/Ethinylestradiol use:
The following conditions have been reported to occur or deteriorate with both pregnancy and use of a COC or oestrogen/progestogen combinations like Cyproterone Acetate/Ethinylestradiol. Consideration should be given to stopping Cyproterone Acetate/Ethinylestradiol if any of the following occur during use:
• jaundice and/or pruritus related to cholestasis
• COCs or Cyproterone Acetate/Ethinylestradiol may increase the risk of gallstone formation and may worsen existing disease
• systemic lupus erythematosus
• herpes gestationis
• otosclerosis-related hearing loss
• sickle cell anaemia
• renal dysfunction
• hereditary angioedema
• any other condition an individual woman has experienced worsening of during pregnancy or previous use of COCs or Cyproterone Acetate/Ethinylestradiol.

Disturbances of liver function
Acute or chronic disturbances of liver function may necessitate the discontinuation of COC or Cyproterone Acetate/Ethinylestradiol use until markers of liver function return to normal

Diabetes (without vascular involvement)
Insulin-dependent diabetics without vascular disease can use Cyproterone Acetate/Ethinylestradiol. However it should be remembered that all diabetics are at an increased risk of arterial disease and this should be considered when prescribing COCs or Cyproterone Acetate/Ethinylestradiol. Diabetics with existing vascular disease are contraindicated from using Cyproterone Acetate/Ethinylestradiol (see section 4.3 Contraindications).

Although COCs or oestrogen/progestogen combinations like Cyproterone Acetate/Ethinylestradiol may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing < 0.05 mg ethinylestradiol). However, diabetic women should be carefully observed while taking COCs or Cyproterone Acetate/Ethinylestradiol.

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

Menstrual Changes
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.

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

Some women may experience amenorrhoea or oligomenorrhoea after discontinuation of Cyproterone Acetate/Ethinylestradiol, especially when these conditions existed prior to use. Women should be informed of this possibility.

Lactose and Sucrose Intolerance
Each tablet of this medicinal product contains 31.115 mg lactose and 19.371 mg sucrose per tablet. Patients with rare

hereditary problems of galactose intolerance, the Lapp lactase deficiency, fructose intolerance or glucosegalactose malabsorption or sucrase-isomaltase should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions

Hepatic enzyme inducers
Drugs which induce hepatic enzymes (especially cytochrome P450 3A4) increase the metabolism of contraceptive steroids and hence may result in breakthrough bleeding and pregnancy. The following have been shown to have clinically important interactions with COCs and oestrogen/progestogen combinations like Cyproterone Acetate/Ethinylestradiol :

Antiretroviral agents
• ritonavir;
• nelfinavir;
• nevirapine.

Anticonvulsants

• barbiturates (including phenobarbitone);
• primidone;
• phenytoin;
• carbamazepine;
• oxcarbazepine;
• topiramate.

Antibiotics/antifungals
• griseofulvin;
• rifampacin.

Herbal remedies
• St John's wort (*Hypericum perforatum*)

Managing the interactions with hepatic enzyme inducers
Since interactions of enzyme inducers, including the antibiotics rafampicin and griseofulvin, with oral contraceptives may lead to breakthrough bleeding and/or contraceptive failure the following precautions are recommended:

Women on short term treatment with any of these drugs should temporarily use a barrier method in addition to the COC or choose another method of contraception. With microsomal enzyme-inducing drugs, such as rifampicin and griseofulvin, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be used.

Non-enzyme inducing antibiotics
Some clinical reports suggest that enterohepatic circulation of oestrogens may decrease when certain antibiotic agents are given, which may reduce ethinylestradiol concentrations (e.g. *penicillins, tetracycline*s).

Managing interactions with non-enzyme inducing antibiotics
Since interactions of some antibiotics with oral contraceptives may lead to breakthrough bleeding and/or contraceptive failure the following precautions are recommended:

Women on short term treatment with antibiotics (except rifampicin and griseofulvin) should temporarily use a barrier method in addition to the COC or choose another method of contraception. If the barrier method is chosen it should be used until 7 days after discontinuation of the antibiotics. 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.

When drugs such as oral tetracyclines are being taken it is 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 Cyproterone Acetate/Ethinylestradiol is being taken.

Effects on other drugs
Oral contraceptives and oestrogen/progestogen combinations like Cyproterone Acetate/Ethinylestradiol may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

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

Laboratory tests
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.

4.6 Fertility, pregnancy and lactation

Cyproterone Acetate/Ethinylestradiol is not indicated during pregnancy. If pregnancy occurs during treatment with Cyproterone Acetate/Ethinylestradiol , further intake must be stopped.

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 the product to women after the 45th day of pregnancy could cause feminisation of male foetuses. It follows from this that pregnancy is an absolute contraindication for treatment with Cyproterone Acetate/Ethinylestradiol , and must be excluded before such treatment is begun.

The use of Cyproterone Acetate/Ethinylestradiol during lactation may lead to a reduction in the volume of milk produced and to a change in its composition. Minute amounts of the active substances are excreted with the milk. These amounts may affect the child particularly in the first 6 weeks post-partum. Mothers who are breast-feeding should be advised not to take Cyproterone Acetate/Ethinylestradiol until the nursing mother has weaned her child off breast milk.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

System organ class	**Adverse events reported in clinical trials**			**Adverse events reported post marketing**
	Common (≥1/100)	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	
Eye disorders			contact lens intolerance	
Gastrointestinal disorders	nausea, abdominal pain	vomiting, diarrhoea		
Immune system disorders			hypersensitivity	Exacerbation of hereditary angioedema

Investigations	weight increased		weight decreased	
Metabolism and nutrition disorders		fluid retention		hypertriglyceridemia
Nervous system disorders	headache	migraine		exacerbation of chorea
Gastrointestinal disorders				Crohn's disease, ulcerative colitis
Hepatobiliary disorders				liver function disturbances
Psychiatric disorders	depressed mood, mood altered	libido decreased	libido increased	
Reproductive system and breast disorders	breast pain, breast tenderness	breast hypertrophy	vaginal discharge, breast discharge	reduced menstrual flow, spotting, breakthrough bleeding and missed withdrawal bleeding, post pill amenorrhoea
Skin and subcutaneous tissue disorders		rash, urticaria	erythema nodosum, erythema multiforme	chloasma

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

The following serious adverse events have been reported in women using COCs or Cyproterone Acetate/Ethinylestradiol, which are discussed in section 4.4 'Special warnings and precautions for use':
• Venous thromboembolic disorders
• Arterial thromboembolic disorders
• Strokes (e.g. transient ischemic attack, ischemic stroke, haemorrhagic stroke)
• Hypertension
• Liver tumours (benign and malignant)

The frequency of diagnosis of breast cancer is very slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC or Cyproterone Acetate/Ethinylestradiol use is unknown. For further information, see sections 4.3 'Contraindications' and 4.4 'Special warnings and precautions for use.

Conditions reported to deteriorate with pregnancy or previous COC or Cyproterone Acetate/Ethinylestradiol use

Jaundice and/or pruritus related to cholestasis; gallstone formation; systemic lupus erythematosus; herpes gestationis; otosclerosis-related hearing loss; sickle cell anaemia; renal dysfunction; hereditary angioedema; porphyria; cervical cancer.

Changes in glucose tolerance or effect on peripheral insulin resistance have been reported in women using COCs or Cyproterone Acetate/Ethinylestradiol (see section 4.4).

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code : G03HB Antiandrogen and Estrogens
01 Cyproterone and estrogen

Cyproterone Acetate/Ethinylestradiol blocks androgen-receptors. It also reduces androgen synthesis both by negative feedback effect on the hypothalamo-pituitiary-ovarian systems and by the inhibition of androgen-synthesising enzymes.

Although Cyproterone Acetate/Ethinylestradiol 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 Cyproterone Acetate/Ethinylestradiol 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 Cyproterone Acetate/Ethinylestradiol was 109% when compared to an aqueous microcrystalline suspension.

Ethinylestradiol: Orally administered ethinylestradiol is rapidly and completely absorbed. Following ingestion of Cyproterone Acetate/Ethinylestradiol 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 coadministered progestin. During treatment with Cyproterone Acetate/Ethinylestradiol 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

Tablet Core
Lactose monohydrate
Maize starch
Povidone K25
Talc
Magnesium stearate

Tablet Coat
Sucrose
Povidone 700 000
Macrogol 6000
Calcium carbonate
Talc
Glycerol 85%
Titanium dioxide (E 171)
Iron oxide pigment yellow (E 172)
Montanglycol wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Keep container in the outer carton.

Do not store above 30°C.

6.5 Nature and contents of container

Blister strips

Polyvinylchloride blisters sealed onto aluminium foil.

Pack sizes
21, 42, 63, 84, 105, 126, 147, 168, 189, 210, 231, 252 tablets (in blister strips of 21 tablets).

Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics (UK) Limited trading as Mylan
Station Close
Potters Bar
Hertfordshire EN6 1TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0405/032/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 09 October 2006

10 DATE OF REVISION OF THE TEXT

December 2012