SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Clairette ▼ 2000/35 Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Actives:	
Cyproterone acetate	2.00 mg
Ethinylestradiol	35 micrograms
Excipients:	
Lactose monohydrate	31.115 mg
Sucrose	19.637 mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sugar-coated tablets
Clairette 2000/35 Tablets are white, biconvex, round tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age.

For the treatment of acne, Clairette 2000/35 Tablets should only be used after topical therapy or systemic antibiotic treatments have failed.

Since Clairette 2000/35 Tablets is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives (see section 4.3)

4.2 Posology and method of administration

Clairette 2000/35 Tablets inhibit ovulation and thereby prevent conception. Patients who are using Clairette 2000/35 Tablets 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 Clairette 2000/35 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 Clairette 2000/35 Tablets, follow the instructions given below:
Changing from 21-day combined oral contraceptives: The first Clairette 2000/35 tablet should be taken on the first day immediately after the end of the previous oral contraceptive course. Additional contraceptive precautions are not required.

Changing from a combined Every Day pill (28 day tablets):

The first Clairette 2000/35 tablet should be taken the day after taking the last active tablet from the Every Day Pill pack. Additional contraceptive precautions are not then required.

Changing from a progestogen-only pill (POP):

The first tablet of Clairette 2000/35 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, Clairette 2000/35 Tablets 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 Clairette 2000/35 Tablets. After a first-trimester abortion, Clairette 2000/35 Tablets may be started immediately in which case no additional contraceptive precautions are required.

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

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.

• Concomitant use with another hormonal contraceptive (see section 4.1)

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

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

• Presence or history of cerebrovascular accident

• The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis (see section 4.4) such as:
    - o diabetes mellitus with vascular symptoms
    - o severe hypertension
    - o severe dyslipoproteinaemia

• Hereditary or acquired predisposition for venous or arterial thrombosis, such as activated protein C (APC) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant)

• History of migraine with focal neurological symptoms.

• 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.

Clairette 2000/35 Tablets 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:
Clairette 2000/35 Tablets is composed of the progestogen cyproterone acetate and the oestrogen ethinylestradiol and is administered for 21 days of a monthly cycle. It has a similar composition to that of a combined oral contraceptive (COC).

Duration of Use
Time to relief of symptoms is at least three months. The need to continue treatment should be evaluated periodically by the treating physician (see section 4.2).

Women should be advised that Clairette 2000/35 Tablets does not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Conditions which require strict medical supervision
If any of the conditions/risk factors mentioned below is present, the benefits of the use of Clairette 2000/35 Tablets should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using Clairette 2000/35 Tablets . In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether the use of Clairette 2000/35 Tablets 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 Clairette 2000/35 Tablets 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 Clairette 2000/35 Tablets.

Reasons for stopping Clairette 2000/35 Tablets 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>

• The use of Clairette 2000/35 Tablets carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman starts Clairette 2000/35 Tablets or when restarting or switching after a pill-free interval of at least a month. Venous thromboembolism can be fatal in 1-2% of cases.

• Epidemiological studies have shown that the incidence of VTE is 1.5 to 2 times higher in users of Clairette 2000/35 Tablets than in users of levonorgestrel-containing combined oral contraceptives (COCs) and may be similar to the risk for desogestrel / gestodene / drospirenone-containing COCs.

• The user group of Clairette 2000/35 Tablets is likely to include patients that may have an inherently increased cardiovascular risk such as that associated with polycystic ovarian syndrome.

• Epidemiological studies have also associated the use of hormonal contraceptive with an increased risk for arterial (myocardial infarction, transient ischaemic attack) thromboembolism.

• Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in hormonal contraceptive users.

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

• The risk of venous thromboembolic events increases with:

- increasing age;

- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age. Women over 35 years of age should be strongly advised not to smoke if they wish to use Clairette 2000/35 Tablets);

- a positive family history (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use;

- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation. Antithrombotic treatment should be considered if the use of Clairette 2000/35 Tablets has not been discontinued in advance.

- obesity (body mass index over 30 kg/m^2).

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

• The risk of arterial thromboembolic complications or of a cerebrovascular accident increases with:

- increasing age;

- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age. Women over 35 years of age should be strongly advised not to smoke if they wish to use Clairette 2000/35 Tablets);

- dyslipoproteinemia;

- obesity (body mass index over 30 kg/m^2);

- hypertension;

- migraine;

- valvular heart disease;

- atrial fibrillation;

- a positive family history (arterial thrombosis ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.

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

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

• An increase in frequency or severity of migraine during use of Clairette 2000/35 Tablets (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of Clairette 2000/35 Tablets .

Women using Clairette 2000/35 Tablets should be specifically pointed out to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, Clairette 2000/35 Tablets use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy (coumarins).

• *Other factors affecting circulatory events*

The user group of Clairette 2000/35 Tablets as a treatment for 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. 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 Clairette 2000/35 Tablets use.

Tumours

Like many other steroids, Clairette 2000/35 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.

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 Clairette 2000/35 Tablets confer protective effects to the same level.

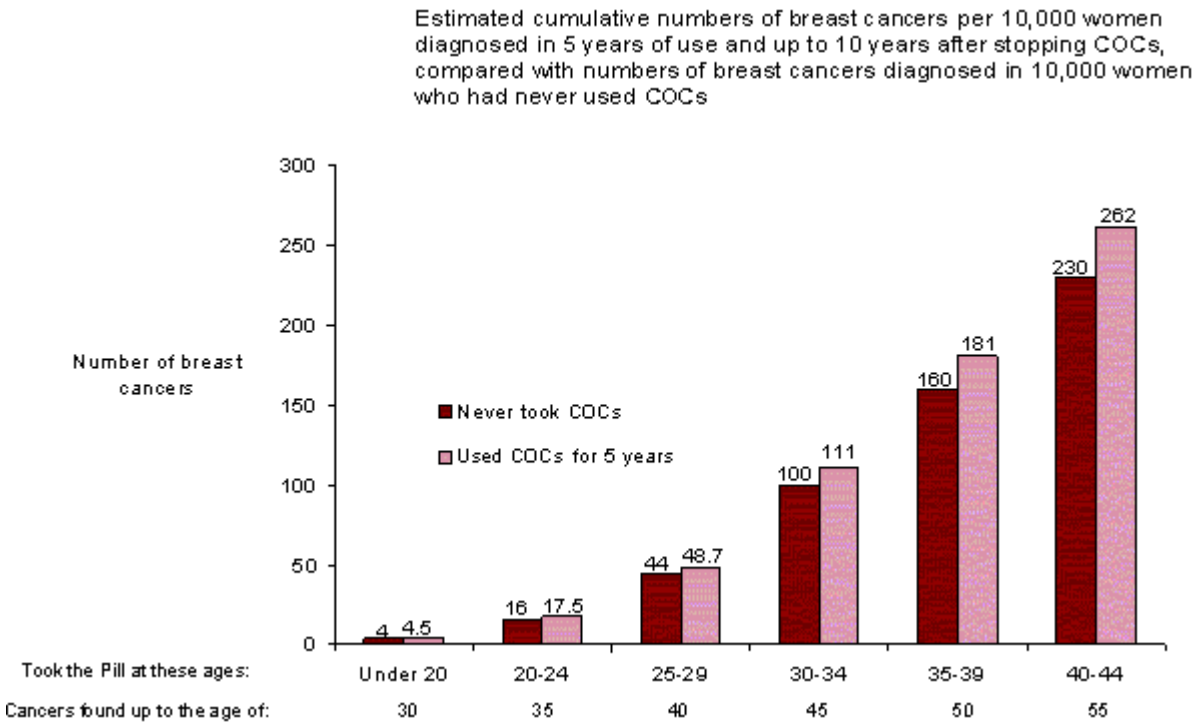
• *Breast cancer*

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).



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 Clairette 2000/35 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.

Other conditions

The possibility cannot be ruled out that certain chronic diseases may occasionally deteriorate during the use of Clairette 2000/35 Tablets .

• *Known hyperlipidaemias*

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs or Clairette 2000/35 Tablets .

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 Clairette 2000/35 Tablets 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 Clairette 2000/35 Tablets , clinically relevant increases are rare. However, if sustained hypertension develops during the use of Clairette 2000/35 Tablets , 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 Clairette 2000/35 Tablets , should be made at lower BP levels, and alternative contraception may be advised.

• *Conditions which deteriorate with pregnancy or during previous COC or Clairette 2000/35 Tablets use:*

The following conditions have been reported to occur or deteriorate with both pregnancy and use of a COC or oestrogen/progestogen combinations like Clairette 2000/35 Tablets. Consideration should be given to stopping Clairette 2000/35 Tablets if any of the following occur during use:

• jaundice and/or pruritus related to cholestasis

• COCs or Clairette 2000/35 Tablets 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 Clairette 2000/35 Tablets.

• *Disturbances of liver function*

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC or Clairette 2000/35 Tablets use until markers of liver function return to normal.

• *Diabetes (without vascular involvement*)

Insulin-dependent diabetics without vascular disease can use Clairette 2000/35 Tablets . 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 Clairette 2000/35 Tablets . Diabetics with existing vascular disease are contraindicated from using Clairette 2000/35 Tablets (see section 4.3 Contraindications).

Although COCs or oestrogen/progestogen combinations like Clairette 2000/35 Tablets 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 Clairette 2000/35 Tablets.

• *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 Clairette 2000/35 Tablets

• *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 Clairette 2000/35 Tablets , 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 19.637 mg sucrose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, fructose intolerance or glucose-galactose 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 Clairette 2000/35 Tablets :

Antiretroviral agents

• ritonavir;

• nelfinavir;

• nevirapine.

Anticonvulsants

• barbiturates (including phenobarbitone);

• primidone;

• phenytoin;

• carbamazepine;

• oxcarbazepine;

• topiramate.

Antibiotics/antifungals

• griseofulvin;

• rifampicin.

Herbal remedies

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

Managing the interactions with hepatic enzyme inducers

Since interactions of enzyme inducers, including the antibiotics rifampicin 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 Clairette 2000/35 Tablets is being taken.

Effects on other drugs

Oral contraceptives and oestrogen/progestogen combinations like Clairette 2000/35 Tablets 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 Pregnancy and lactation

Clairette 2000/35 Tablets is not indicated during pregnancy. If pregnancy occurs during treatment with Clairette 2000/35 Tablets , 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 Clairette 2000/35 Tablets 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 Clairette 2000/35 Tablets , and must be excluded before such treatment is begun.

The use of Clairette 2000/35 Tablets 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 Clairette 2000/35 Tablets 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 (≥ 1/1000, <1/100)**	**Rare (≥ 1/10,000 to < 1/1000)**	
Eye disorders			contact lens intolerance	
Gastrointestinal disorders	nausea, abdominal pain	vomiting, diarrhea		
Immune system			hypersensitivity	Exacerbation of hereditary

disorders				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
Vascular Disorders			Thromboembolism	

Post-marketing reports of severe depression in patients using Clairette 2000/35 Tablets have been received. However, a causal relationship between clinical depression and Clairette 2000/35 Tablets has not been established.

There is an increased risk of thromboembolism for all women who use Clairette 2000/35 Tablets (see section 4.4)

The following serious adverse events have been reported in women using Clairette 2000/35 Tablets , 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 Clairette 2000/35 Tablets 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 Clairette 2000/35 Tablets 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 Clairette 2000/35 Tablets (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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

Clairette 2000/35 Tablets 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 Clairette 2000/35 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 in a wide dose range. The ingestion of Clairette 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 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 pre-clinical safety data which could be of relevance to the prescriber and which are not already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Maize starch, Povidone K 25, Magnesium stearate, Talc, Sucrose, Calcium carbonate, Macrogol 6000, Titanium dioxide (E171), Povidone K 90, Glycerol 85%, Wax (montan glycol)

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4. Special precautions for storage

No special storage precautions. Store in the original package.

6.5. Nature and contents of container

Packs of blister strips (aluminium foil/PVC) containing 21 or 63 tablets

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Stragen UK Limited
Castle Court
41 London Road
Reigate
Surrey
RH2 9RJ
UK

8. MARKETING AUTHORISATION NUMBER

PL 21844/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

07/01/2014