GINETTE 35 Tablets (Cyproterone acetate + Ethinylestradiol)

To be sold by retail on the prescription of RMP only

Qualitative and Quantitative Composition

Each film-coated tablet contains:

Cyproterone acetate … 2 mg

Ethinylestradiol … 0.035 mg

Dosage Form and Strength

Cyproterone acetate 2 mg and Ethinylestradiol 0.035 mg tablets for oral use.

Clinical Particulars

Therapeutic Indications

GINETTE 35 is indicated for the treatment of androgen-dependent disease in women such as acne, alopecia and mild form of hirsutism.

Posology and Method of Administration

GINETTE 35 inhibits ovulation and, thereby, prevents conception. Patients who are using **GINETTE 35** 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 following the arrows, 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 **GINETTE 35** 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 **GINETTE 35**, follow the instructions given below.

Changing from 21-Day Combined Oral Contraceptives (COCs)

The first tablet of **GINETTE 35** should be taken on the first day immediately after the end of the previous COC course. Additional contraceptive precautions are not required.

Changing from a Combined Every Day Pill (28 day tablets)

GINETTE 35 should be started after taking the last hormone containing tablet from the Every Day Pill pack. The first tablet of **GINETTE 35** is taken the next day. Additional contraceptive precautions are not then required.

Changing from a Progestogen- only Pill (POP)

The first tablet of **GINETTE 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 POPs should be discarded.

Postpartum and Post-abortum Use

After pregnancy, **GINETTE 35** 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 tablet taking. Since the first postpartum ovulation may precede the first bleeding, another method of contraception should be used in the interval between childbirth and the first course of tablets. Lactation is contraindicated with **GINETTE 35**. After a first trimester abortion, **GINETTE 35** 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 the days a tablet is taken, but this is not clinically significant. If the patient does not have a withdrawal bleed during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be ruled out before starting the next pack.

Gastrointestinal Upset

Vomiting or diarrhoea may reduce the efficacy of oral contraceptives by preventing full absorption. Tablets from the current pack should be continued. Additional non-hormonal methods of contraception (except the rhythm or temperature methods) should be used during the gastrointestinal upset and for 7 days following the upset. If these 7 days overrun the end of a pack, the next pack should be started without a break. In this situation, a withdrawal bleed should not be

expected until the end of the second pack. If the patient does not have a withdrawal bleed during 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 gastrointestinal disorder is likely to be prolonged.

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.
- Venous thrombosis present or in history (e.g. 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 such as:
  - diabetes mellitus with vascular symptoms
  - severe hypertension
  - 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
- Breastfeeding
- Hypersensitivity to the active substances or to any of the excipients

Cyproterone acetate + Ethinylestradiol (CPA+EE) is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir or dasabuvir.

CPA+EE is not for use in men.

Special Warnings and Precautions of Use

General

This product is composed of the progestogen CPA and the oestrogen EE and is administered for 21 days of a monthly cycle. It has a similar composition to that of a COC.

Duration of Use

Time to relief of symptoms is at least 3 months. The need to continue treatment should be evaluated periodically by the treating physician.

Women should be advised that CPA+EE does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

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 and warnings 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.

Conditions That Require Strict Medical Supervision

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

- Diabetes mellitus, with mild vascular disease or mild nephropathy, retinopathy or neuropathy
- Hypertension that is adequately controlled, i.e. systolic > 140–159 mmHg or diastolic > 90–94 mmHg
- 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 CPA+EE.

Reasons for Stopping CPA+EE Immediately

When stopping oral contraception, non-hormonal contraception should be used to ensure contraceptive protection is maintained, if needed.

- Occurrence for the first time, or exacerbation, of migrainous headaches or unusually frequent or unusually severe headaches.
- Sudden disturbances of vision or hearing or other perceptual disorders.
- 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.
- Six weeks before an elective major operation (e.g. abdominal, orthopaedic), any surgery to the legs, medical treatment for varicose veins or prolonged immobilization, 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.
- Onset of jaundice, hepatitis, itching of the whole body.
- Significant rise in blood pressure.
- Onset of severe depression.
- Severe upper abdominal pain or liver enlargement.

- Clear worsening of conditions known to deteriorate during use of hormonal contraception or during pregnancy.
- Pregnancy.

Circulatory Disorders

- The use of CPA+EE 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 CPA+EE or when restarting or switching after a pill-free interval of at least a month. VTE is fatal in 1–2% of cases.
- Epidemiological studies have shown that the incidence of VTE is 1.5–2 times higher in users of CPA+EE than in users of levonorgestrel-containing COCs and may be similar to the risk for desogestrel/gestodene/drospirenone-containing COCs.
- The user group of CPA+EE is likely to include patients that may have an inherently increased cardiovascular risk such as that associated with polycystic ovarian syndrome (PCOS).
- 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 the following:
  - 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 CPA+EE);
  - A positive family history (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.
  - Prolonged immobilization, 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 4 weeks in advance) and not to resume until 2 weeks after complete remobilization. Antithrombotic treatment should be considered if the use of CPA+EE has not been discontinued in advance.
  - Obesity (body mass index > 30 kg/m^2)

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

- 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 CPA+EE)
  - 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.
  - Obesity (body mass index > 30 kg/m^2)
  - Dyslipoproteinaemia

- Hypertension
- Valvular heart disease
- Atrial fibrillation
- Migraine

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

The increased risk of thromboembolism in the puerperium must be considered.

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

Women using CPA+EE should be specifically pointed out to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, CPA+EE 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 CPA+EE 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 PCOS.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include 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 CPA+EE use.

Tumours

Like many other steroids, CPA+EE 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 COCs. The evidence is clear that high dose COCs offer substantial protection against both ovarian and endometrial cancer. However, it is not clear whether low dose COCs or CPA+EE 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 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 localized 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).

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 CPA+EE. 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 CPA+EE.

Known Hyperlipidaemias

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs or CPA+EE.

Women with hyperlipidaemias are at an increased risk of arterial disease. However routine screening of women on COCs or CPA+EE is not appropriate.

Blood Pressure

Hypertension is a risk factor for stroke and myocardial infarction. Although small increases in blood pressure have been reported in many women taking COCs or oestrogen/progestogen combinations like CPA+EE, clinically relevant increases are rare. However, if sustained hypertension develops during the use of CPA+EE, 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 CPA+EE should be made at lower BP levels, and alternative contraception may be advised.

Conditions That Deteriorate with Pregnancy or During Previous COC or CPA+EE Use

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

- Jaundice and/or pruritus related to cholestasis
- COCs or CPA+EE 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 angio-oedema
- Epilepsy
- Any other condition an individual woman has experienced worsening of during pregnancy or previous use of COCs or CPA+EE.

Disturbances of Liver Function

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC or CPA+EE use until markers of liver function return to normal.

Diabetes (Without Vascular Involvement)

Insulin-dependent diabetics without vascular disease can use CPA+EE. 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 CPA+EE. Diabetics with existing vascular disease are contraindicated from using CPA+EE.

Although COCs or oestrogen/progestogen combinations like CPA+EE 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 EE). However, diabetic women should be carefully observed while taking COCs or CPA+EE.

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 CPA+EE.

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 CPA+EE, especially when these conditions existed prior to use. Women should be informed of this possibility.

ALT elevations

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using EE-containing medications such as combined hormonal contraceptives (CHC).

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.

Drug Interactions

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

Enzyme Inducers

Interactions can occur with drugs that induce microsomal enzymes (especially cytochrome P4503A4) which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

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. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond 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.

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

The following have been shown to have clinically important interactions with CPA+EE:

- 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)

Note: There are other antiretroviral agents that may increase plasma concentration of sex hormones.

Substances decreasing the Clearance of CHC (Enzyme Inhibitors)

The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the oestrogen or the progestin or both.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0.035 mg ethinylestradiol.

Effects of Oestrogen/Progestogen Combinations on Other Drugs

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

Pharmacodynamic interactions

Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations.

Therefore, CPA+EE-users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. CPA+EE can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Clinical data suggest that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

Use in Special Populations

Patients with renal impairments

CPA+EE has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

Patients with hepatic impairment

CPA+EE is contraindicated in women with severe hepatic disease as long as liver function values have not returned to normal.

Pregnant women

CPA+EE is not indicated during pregnancy. If pregnancy occurs during treatment with CPA+EE, further intake must be stopped.

Animal studies have revealed that feminization of male foetuses may occur if CPA 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 humans, the possibility must be considered that administration of CPA+EE to women after the 45th day of pregnancy could cause feminization of male foetuses. It follows from this that pregnancy is an absolute contraindication for treatment with CPA+EE and must be excluded before such treatment is begun.

Lactating women

The use of CPA+EE 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 postpartum. Mothers who are breastfeeding should be advised not to take CPA+EE until the nursing mother has weaned her child off breast milk.

Paediatric Patients

CPA+EE is only indicated after menarche.

Geriatric patients

CPA+EE is not indicated after menopause.

Effects on Ability to Drive and Operate Heavy Machinery

CPA + EE has no known effect on the ability to drive or use machines.

Undesirable Effects

The most commonly reported adverse reactions with CPA+EE are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. They occur in ≥ 1 % of users.

There is an increased risk of thromboembolism for all women who use CPA+EE.

Tabulated list of adverse events:

System Organ Class	Adverse Events Reported in Clinical Trials			Adverse Events Reported Post-Marketing
	Common (1/100 to <1/10)	Uncommon (1/1000, <1/100)	Rare (≥1/10,000 to < 1/1000)	
Eye Disorders			Contact lens intolerance	
Gastrointestinal Disorders	Nausea, Abdominal pain	Vomiting, Diarrhoea		Crohn's disease, Ulcerative colitis
Immune System Disorders			Hypersensitivity	Exacerbation of hereditary angio-oedema
Investigations	Weight increased		Weight decreased	

Metabolism and Nutrition Disorders		Fluid retention		Hypertriglycerid-aemia
Nervous System Disorders	Headache	Migraine		Exacerbation of chorea
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	Increase in blood pressure

Post-marketing reports of severe depression (including very rare reports of suicidal ideation or behaviour) in patients using CPA+EE have been received. However, a causal relationship between clinical depression and CPA+EE has not been established.

An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs.

The following serious adverse events have been reported in women using CHCs.

- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Hypertension
- Liver tumours
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, uterine myoma, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice;
- Chloasma;
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.
- In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.

The frequency of diagnosis of breast cancer is very slightly increased among COC 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 CPA+EE use is unknown.

Interactions

Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with oral contraceptives.

Reporting of side effects

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779. By reporting side effects, you can help provide more information on the safety of this product.

Overdose

Overdose may cause nausea, vomiting and withdrawal bleeding. Withdrawal bleeding may even occur in girls before their menarche, if they accidentally take the medicinal product. There are no specific antidotes and further treatment should be symptomatic.

Pharmacological Properties

Mechanism of Action

Cyproterone acetate is a competitive antagonist on the androgen receptor, has inhibitory effects on the androgen-synthesis in target cells and produces a decrease on the androgen blood concentration through an anti-gonadotropic effect. This anti-gonadotropic effect is amplified by ethinylestradiol which also up-regulates the synthesis of Sex-Hormone-Binding Globulin (SHBG) in plasma. By this mechanism, it reduces free, biologically available androgen in the circulation.

Pharmacodynamic Properties

GINETTE 35 (CPA+EE) 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-synthesizing enzymes.

Although **GINETTE 35** 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 conditions described.

Pharmacokinetic Properties

Cyproterone Acetate

Following oral administration, CPA is completely absorbed in a wide dose range. The ingestion of CPA+EE attains a maximum serum level of 15 ng CPA /ml at 1.6 hours. Thereafter, drug serum levels decrease in two disposition phases characterized by half-lives of 0.8 hours and 2.3 days. The total clearance of CPA from serum was determined to be 3.6 ml/min/kg. CPA is metabolized by various pathways, including hydroxylations and conjugations. The main metabolite in human plasma is the 15 beta-hydroxy derivative.

Some dose parts are excreted unchanged with the bile fluid. Most of the dose is excreted in the form of metabolites at a urinary to biliary ratio of 3:7. The renal and biliary excretion was determined to proceed with a half-life of 1.9 days. Metabolites from plasma were eliminated at a similar rate (half-

life of 1.7 days). CPA 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 CPA pharmacokinetics.

According to the long half-life of the terminal disposition phase from plasma (serum) and the daily intake, CPA accumulates during one treatment cycle. Mean maximum drug serum levels increased from 15 ng/ml (day 1) to 21 ng/ml and 24 ng/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, CPA accumulates over treatment cycles by a factor of 2.

The absolute bioavailability of CPA is almost complete (88% of dose). The relative bioavailability of CPA from CPA+EE was 109% when compared to an aqueous microcrystalline suspension.

Ethinylestradiol

Orally administered EE is rapidly and completely absorbed. Following ingestion of CPA+EE, maximum drug serum levels of about 80 pg/ml are reached at 1.7 hours. Thereafter, EE plasma levels decrease in two phases characterized by half-lives of 1–2 hours and about 20 hours. For analytical reasons, these parameters can only be calculated for higher dosages.

For EE, 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.

EE is highly but non-specifically bound to serum albumin. 2% of the drug levels are present unbound. During absorption and first liver passage, EE is metabolized resulting in a reduced absolute and variable oral bioavailability. Unchanged drug is not excreted. EE 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 EE was almost complete.

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

EE 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 CPA+EE, SHBG concentrations in serum increased from about 100–300 nmol/l and the serum concentrations of CBG were increased from about 50–95 mcg/ml.

In vitro, Ethinyl estradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8 and CYP2J2.

Non-Clinical Properties

Animal Toxicology and Pharmacology

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 Prescribing Information.

Description

GINETTE 35 is an oral contraceptive indicated for the treatment of androgen-dependent disease in women. Each pack consists of 21 tablets and each tablet contains 2 mg of cyproterone acetate (CPA) and 0.035 mg of ethinylestradiol (EE).

Pharmaceutical Particulars

Incompatibilities

Not available

Shelf life

As on pack

Packaging Information

GINETTE 35 is available in a blister pack of 21 tablets

Storage and Handling Information

Store in a dark place at a temperature not exceeding 25°C.

Patient Counselling Information

What is GINETTE 35 and what it is used for?

GINETTE 35 contains an oestrogen and an anti-androgen.

GINETTE 35 is used to treat skin conditions such as acne, very oily skin and excessive hair growth in women of reproductive age. Due to its contraceptive properties it should only be prescribed for you if your doctor considers that treatment with a hormonal contraceptive is appropriate.

You should only take **GINETTE 35** if your skin condition has not improved after use of other anti-acne treatments, including topical treatments and antibiotics.

If you are taking **GINETTE 35** for skin treatment, **you must not take any other hormonal contraceptive at the same time**.

When your skin condition has cleared up and you stop taking **GINETTE 35**, you will need to go back to your original/preferred method of contraception.

Treating skin conditions

Androgens are hormones that stimulate hair growth and the grease glands in your skin. If you produce too much androgen, or if you are sensitive to the effect, the grease glands may produce too much sebum. This can block the grease glands, which can become infected and inflamed causing acne spots. **GINETTE 35** stops the androgens affecting your skin and reduces the amount of androgens produced.

Contraception

GINETTE 35 is a 21-day Pill – you take one each day for 21 days, followed by 7 days when you take no pills. **GINETTE 35** will not protect you against sexually transmitted infections, such as Chlamydia or HIV. Only condoms can help to do this.

GINETTE 35 needs to be taken as directed to prevent pregnancy.

What You Need To Know Before You Take Ginette 35

Before you take GINETTE 35

It's important that you understand the benefits and risks of taking **GINETTE 35** before you start taking it, or when deciding whether to carry on taking it. Although **GINETTE 35** is suitable for most healthy women it isn't suitable for everyone.

◦ **Tell your doctor if** you have any of the illnesses or risk factors mentioned in this leaflet.

Before you start taking GINETTE 35

Your doctor will ask about you and your family's medical problems and check your blood pressure and exclude the likelihood of you being pregnant. You may also need other checks, such as a breast examination, but only if these examinations are necessary for you or if you have any special concerns.

While you're on GINETTE 35

You will need **regular check-ups** with your doctor, usually when you need another prescription of **GINETTE 35.**

You should go for regular **cervical smear tests**.

Check your breasts and nipples every month for changes – tell your doctor if you can see or feel anything odd, such as lumps or dimpling of the skin.

If you need a blood test tell your doctor that you are taking **GINETTE 35**, because this type of medicine can affect the results of some tests.

If you're going to have an operation, make sure your doctor knows about it. You may need to stop taking **GINETTE 35** about 4–6 weeks before the operation. This is to reduce the risk of a blood clot. Your doctor will tell you when you can start taking **GINETTE 35** again.

If you need to stop taking GINETTE 35, remember to use another contraceptive (e.g. condoms) if you are relying on **GINETTE 35** for contraception.

When Should You Contact Your Doctor

Stop taking CPA +EE and contact your doctor immediately if you notice possible signs of a blood clot. The symptoms are described below in 'Blood clots (Thrombosis)'

CPA + EE also works as an oral contraceptive. You and your doctor will have to consider all the things that would normally apply to the safe use of oral hormonal contraceptives.

Blood clots (thrombosis)

Taking **CPA + EE** may slightly increase your risk of having a blood clot (called a thrombosis). Your

chances of having a blood clot are only increased slightly by taking **CPA + EE** compared with women who do not take **CPA + EE** or any contraceptive pill. A full recovery is not always made and in 1-2% of cases, can be fatal.

Blood clots in a vein

A blood clot in a vein (known as a 'venous thrombosis') can block the vein. This can happen in veins of the leg, the lung (a lung embolus), or any other organ.

Using a combined pill increases a woman's risk of developing such clots compared with a woman not taking any combined pill. The risk of developing a blood clot in a vein is highest during the first year a woman uses the pill. The risk is not as high as the risk of developing a blood clot during pregnancy.

Your chances of having a blood clot are only increased slightly by taking **CPA + EE**

- Of 100,000 women who are not taking **CPA + EE**, not on the Pill and not pregnant, about 5 to 10 will have a blood clot in a year.
- Of 100,000 women who take **CPA + EE** or the Pill, up to 40 will have a blood clot in a year.
- Of 100,000 women who are pregnant, around 60 will have a blood clot in a year

The risk of blood clots in a vein in users of a combined pill increases further:

- with increasing age;
- if you smoke.

When using a hormonal contraceptive like **CPA + EE** you are strongly advised to stop smoking, especially if you are older than 35 years;

- if one of your close relatives has had a blood clot in the leg, lung or other organ at a young age;
- if you are overweight;
- if you must have an operation, or if you are off your feet for a long time because of an injury or illness, or you have your leg in a plaster cast;
- if you have polycystic ovary syndrome;
- if you have recently had a baby;
- if you have certain rare medical conditions such as systemic lupus erythematosus, Crohn's disease or ulcerative colitis;
- if you have sickle cell disease.

If this applies to you, it is important to tell your doctor that you are using **CPA + EE**, as the treatment may have to be stopped. Your doctor may tell you to stop using **CPA + EE** several weeks before surgery or while you are less mobile. Your doctor will also tell you when you can start using **CPA + EE** again after you are back on your feet.

Blood clots in an artery

A blood clot in an artery can cause serious problems. For example, a blood clot in an artery in the heart may cause a heart attack, or in the brain may cause a stroke.

The use of a combined pill has been connected with an increased risk of clots in the arteries.

This risk increases further:

- with increasing age;
- if you smoke.
- when using a hormonal contraceptive like **CPA + EE** you are strongly advised to stop smoking, especially if you are older than 35 years;
- if you are overweight;
- if you have high blood pressure;
- if a close relative has had a heart attack or stroke at a young age;
- if you have a high level of fat in your blood (cholesterol or triglycerides);
- if you get migraines;
- if you have a problem with your heart (valve disorder, disturbance of the rhythm);
- if you have polycystic ovary syndrome;
- if you have diabetes;
- if you have certain rare medical conditions such as systemic lupus erythematosus;
- if you have sickle cell disease.

Symptoms of blood clots

Stop taking tablets and see your doctor immediately if you notice possible signs of a blood clot, such as:

- an unusual sudden cough;
- severe pain in the chest which may reach the left arm;
- breathlessness;
- any unusual, severe, or long-lasting headache or worsening of migraine;
- partial or complete loss of vision, or double vision;
- slurring or speech disability;
- sudden changes to your hearing, sense of smell, or taste;
- dizziness or fainting;
- weakness or numbness in any part of your body;
- severe pain in your abdomen;
- severe pain or swelling in either of your legs.

Following a blood clot, recovery is not always complete. Rarely serious permanent disabilities may occur or the blood clot may even be fatal.

Directly after giving birth, women are at an increased risk of blood clots so you should ask your doctor how soon after delivery you can start taking **CPA + EE**

See a doctor straight away if you also develop severe depression, a severe allergic reaction, worsening of hereditary angioedema, signs of breast cancer or cervical cancer or signs of severe liver problems.

CPA + EE and cancer

While high dose COCs reduce your risk of cancer of the ovary and womb if used in the long term, it is not clear whether lower dose oestrogen-progestogen containing Pills like **CPA+EE** also provide the same protective effects. However, it also seems that taking **CPA+EE** slightly increases your risk of cancer of the cervix – although this may be due to having sex without a condom, rather than **CPA+EE.** All women should have regular smear tests.

If you have breast cancer, or have had it in the past, you should not take **CPA+EE** or other oral contraceptives, as they slightly increase your risk of breast cancer. This risk goes up the longer

you're on **CPA+EE** but returns to normal within about 10 years of stopping it. Because breast cancer is rare in women under the age of 40, the extra cases of breast cancer in current and recent **CPA+EE** users is small. For example:

- Of 10,000 women who have never taken **CPA + EE** or the Pill, about 16 will have breast cancer by the time they are 35 years old.
- Of 10,000 women who take **CPA + EE** or the Pill for 5 years in their early twenties, about 17–18 will have breast cancer by the time they are 35 years old.
- Of 10,000 women who have never taken **CPA + EE** or the Pill, about 100 will have breast cancer by the time they are 45 years old.
- Of 10,000 women who take **CPA + EE** or the Pill for 5 years in their early thirties, about 110 will have breast cancer by the time they are 45 years old.

Your risk of breast cancer is higher

- if you have a close relative (mother, sister or grandmother) who has had breast cancer
- if you are seriously overweight

See a doctor as soon as possible if you notice any changes in your breasts, such as dimpling of the skin, changes in the nipple or any lumps you can see or feel.

Taking **CPA + EE** has also been linked to liver diseases, such as jaundice and noncancer liver tumours, but this is rare. Very rarely, **CPA + EE** has also been linked with some forms of liver cancer in women who have taken it for a long time.

See a doctor as soon as possible if you get severe pain in your stomach, or yellow skin or eyes (jaundice). You may need to stop taking **CPA+EE**.

Make sure GINETTE 35 is OK for you

GINETTE 35 should not be taken by some women.

Tell your doctor if you have any medical problems or illnesses.

Do not use CPA +EE.

Tell your doctor if any of the following conditions applies to you before starting to use CPA + EE. Your doctor may then advise you to use a different treatment:

- If you are using another hormonal contraceptive
- If you are pregnant or might be pregnant
- If you are breast-feeding
- If you have or have ever had breast cancer
- If you have (or have ever had) a blood clot in your leg (thrombosis), lung (pulmonary embolism) or other part of your body.
- If you have (or have ever had) a disease that may be an indicator of a heart attack in the future (e.g. angina pectoris which causes severe pain in the chest) or 'ministroke' (transient ischaemic attack)
- If you have (or have ever had) a heart attack or stroke.
- If you have a condition that may increase the risk of a blood clot in your arteries. This applies to the following conditions:
  - diabetes affecting your blood vessels
  - very high blood pressure

    - a very high level of fat in your blood (cholesterol or triglycerides)
- If you have problems with blood clotting (e.g. protein C deficiency)
- If you have (or have ever had) a migraine, with visual disturbances
- If you have ever had a severe liver disease, and you have been told by your doctor that your liver test results are not yet back to normal
- If you have ever had liver tumours
- If you are allergic (hypersensitive) to any of the active ingredients or excipients

Do not use **CPA + EE** if you have hepatitis C and are taking the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir.

If you suffer from any of these or get them for the first time while taking **CPA +EE**, contact your doctor as soon as possible. Do not take **CPA +EE**. If needed, use another form of contraception.

CPA +EE can make some illnesses worse.

Some of the conditions listed below can be made worse by taking **CPA +EE**. Or they may mean it is less suitable for you. You may still be able to take **CPA +EE** but you need to take special care and have check-ups more often.

- If you or your close family have ever had problems with your heart or circulation, such as high blood pressure
- If you or your close family have ever had problems with blood clotting
- If you have had migraines
- If you are currently suffering from depression or have done so in the past
- If you are overweight (obese)
- If you have the inherited disease called porphyria
- If you have diabetes
- If you have inflammation of the pancreas (pancreatitis), or a history or family history of high levels of fat in your blood (hypertriglyceridemia), as you may be at risk of developing pancreatitis
- If you have brown patches on your face or body (chloasma)
- If you have any illness that worsened during pregnancy or previous use of the Pill or **CPA +EE.**

Tell your doctor if any apply to you. Also tell them if you get any of these for the first time while taking **CPA +EE**, or if any get worse or come back, because you may need to stop taking it.

Psychiatric disorders

Some women using hormonal contraceptives including **CPA +EE** have reported depression or depressed mood. Depression can be serious and may sometimes lead to suicidal thoughts. If you experience mood changes and depressive symptoms contact your doctor for further medical advice as soon as possible.

Taking other medicines

Always tell your doctor which medicines or herbal products you are already using. Also tell any other doctor or dentist who prescribes another medicine (or the pharmacist) that you take **GINETTE 35**. They can tell you if you need to take additional contraceptive precautions (for example condoms) and if so, for how long, or, whether the use of another medicine you need must be changed.

Also check the leaflets that come with all your medicines to see if they can be taken with hormonal contraceptives.

If you are taking **GINETTE 35** for skin treatment, you must not take any other hormonal contraceptive at the same time.

Some medicines:

- can have an influence on the blood levels of **CPA+EE** and
- can make it less effective in preventing pregnancy, or
- can cause unexpected bleeding.

These include:

- Medicines used for the treatment of
  - epilepsy (e.g. primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine)
  - tuberculosis (e.g. rifampicin)
  - HIV and Hepatitis C Virus infections (so-called protease inhibitors and nonnucleoside reverse transcriptase inhibitors, such as ritonavir, nevirapine, efavirenz)
  - fungal infections (e.g. griseofulvin, ketoconazole) arthritis, arthrosis (etoricoxib) high blood pressure in the blood vessels in the lungs (bosentan)
- The herbal remedy St. John's wort

If you do need to take one of these medicines, **CPA+EE** may not be suitable for you or you may need to use extra contraception for a while. Your doctor can tell you if this is necessary and for how long.

CPA +EE may influence the effect of other medicines, e.g.

- medicines containing ciclosporin
- the anti-epileptic lamotrigine (this could lead to an increased frequency of seizures)
- theophylline (used to treat breathing problems)
- tizanidine (used to treat muscle pain and/or muscle cramps). Your doctor may need to adjust the dose of your other medicine.

In addition, **CPA+EE** can also interfere with the results of some blood tests, so always tell your doctor that you are taking **CPA+EE** if you have a blood test.

Do not use **CPA+EE** if you have hepatitis C and are taking the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir as this may cause increases in liver function blood test results (increase in ALT liver enzyme). Your doctor will prescribe another type of contraceptive prior to start of the treatment with these medicinal products. **CPA+EE** can be restarted approximately 2 weeks after completion of treatment. See section 'Do not use **CPA+EE** …').

Taking GINETTE 35 with food and drink

There are no special instructions about food and drink while on **CPA+EE.**

Pregnancy and breastfeeding

Do not use CPA+EE if you are pregnant or are breast-feeding. If you think you might be pregnant, do a pregnancy test to confirm that you are before you stop taking **CPA+EE**.

Driving and using machines

CPA +EE has no known effect on the ability to drive or use machines.

CPA +EE and sun-beds or sun-lamps

Sun-lamps are used by some women for acne as well as to tan the skin. This is not a very useful treatment for acne. Do not use sun-beds or sun-lamps and avoid prolonged sunbathing if you are taking **CPA + EE**. Their use increases the chance of chloasma, a patchy discolouration of the skin (as it does with ordinary oral contraceptives).

TAKING GINETTE 35

Your doctor has chosen **GINETTE 35** as a treatment for your acne or excessive hair growth on your face and body. However, **GINETTE 35** also has a contraceptive effect, so it is important to follow the advice below if you are relying on **GINETTE 35** for contraception. If you are only using **GINETTE 35** for your acne or excessive hair growth, you can still follow this advice, but ask your doctor if you are unsure.

Duration of use

Your doctor will tell you how long you need to keep taking **GINETTE 35**.

***How to take* it**

Take GINETTE 35 every day for 21 days

GINETTE 35 comes in strips of 21 pills, each marked with a day of the week.

- Take your pill at the same time every day.
- Start by taking a pill marked with the correct day of the week.
- Follow the direction of the arrows on the strip.
- Take one pill each day, until you have finished all 21 pills.
- Swallow each pill whole, with water if necessary. Do not chew the pill.

Then have seven pill-free days

After you have taken all 21 pills in the strip, you have seven days when you take no pills. Within a few days of taking the last pill from the strip, you should have a withdrawal bleed like a period. This bleed may not have finished when it is time to start your next strip of pills.

If you are relying on this medicine to prevent pregnancy, always take **GINETTE 35** as described here. You don’t need to use extra contraception during the seven pill-free days – as long as you have taken your pills correctly and start the next strip of pills on time. Check with your doctor if you are not sure.

Start your next strip on day eight

Start taking your next strip of **GINETTE 35** after the seven pill-free days (on day eight) – even if you are still bleeding. So if you take the last pill of one pack on a Friday, you will take the first pill of your next pack on the Saturday of the following week. Always start the new strip on time.

As long as you take **GINETTE 35** correctly, you will always start each new strip on the same day of the week.

Starting GINETTE 35

New users or starting **GINETTE 35** after a break. It is best to take your first **GINETTE 35** pill on

the first day of your next period. By starting in this way, you will have contraceptive protection with your first pill.

Changing to **GINETTE 35** from another contraceptive Pill

- If you are currently taking a 21-day Pill: start **GINETTE 35** the next day after the end of the previous strip. You will have contraceptive protection with your first pill. You will not have a bleed until after your first strip of **GINETTE 35**
- If you are taking a 28-day Pill: Start taking **GINETTE 35** the day after your last active pill. You will have contraceptive protection with your first pill. You will not have a bleed until after your first strip of **GINETTE 35**
- If you are taking a progestogen-only Pill (POP or 'mini Pill'): Start **GINETTE 35** on the first day of bleeding, even if you have already taken the progestogen-only Pill for that day. You will have contraceptive cover straight away.

Starting GINETTE 35 after a miscarriage or abortion

If you have had a miscarriage or an abortion **during the first three months** of pregnancy, your doctor may tell you to start taking **GINETTE 35** straight away. This means that you will have contraceptive protection with your first pill. If you have had a miscarriage or an abortion **after the third month of pregnancy**, ask your doctor for advice. You may need to use extra contraception, such as condoms, for a short time.

Contraception after having a baby

If you have just had a baby, your doctor may advise you that **GINETTE 35** should be started 21 days after delivery provided that you are fully mobile. You do not have to wait for a period. You will need to use another method of contraception, such as a condom, until you start **GINETTE 35** and for the first 7 days of pill taking.

Do not take GINETTE 35 if you are breastfeeding.

A missed pill

- If you are less than 12 hours late with a pill, take it straight away. Keep taking your pills at the usual time. This may mean taking two pills in one day. Don't worry – your contraceptive protection should not be reduced.
- If you are more than 12 hours late with a pill, or you have missed more than one pill, your contraceptive protection may be reduced.
- Take the most recently missed pill as soon as you remember, even if it means taking two at once. Leave any earlier missed pills in the pack.

Continue to take a pill every day for the next seven days at your usual time.

If you come to the end of a strip of pills during these seven days, start the next strip without taking the usual seven day break. You probably won't have a bleed until after you finish the second strip of pills, but don't worry. If you finish the second strip of pills and don't have a bleed, do a pregnancy test before starting another strip.

Use extra contraception for seven days after missing a pill, such as condoms. Ø If you have missed one or more pills from the first week of your strip (days 1 to 7) and you had sex in that week, you could become pregnant. Contact your doctor or pharmacist for advice as soon as possible. They may recommend you use emergency contraception.

If you have missed any of the pills in a strip, and you do not bleed in the first pill free break, you may be pregnant.

Contact your doctor or do a pregnancy test yourself.

If you start a new strip of pills late or make your 'week off' longer than seven days, you may not be protected from pregnancy. If you had sex in the last seven days, ask your doctor or pharmacist for advice. You may need to consider emergency contraception. You should also use extra contraception, such as a condom, for seven days.

A lost pill

If you lose a pill,

- **Either** take the last pill of the strip in place of the lost pill. Then take all the other pills on their proper days. Your cycle will be one day shorter than normal, but your contraceptive protection won't be affected. After your seven pill-free days you will have a new starting day, one day earlier than before.
- **Or**, if you do not want to change the starting day of your cycle, take a pill from a spare strip if you have one. Then take all the other pills from your current strip as usual. You can then keep the opened spare strip in case you lose any more pills.

If you are sick or have diarrhea

If you are sick (vomit) or have very bad diarrhea, your body may not get its usual dose of hormones from that pill. If you are better within 12 hours of taking **GINETTE 35**, follow the instructions that are mentioned for A lost pill, which describes how to take another pill.

If you are still sick or have diarrhea more than 12 hours after taking **GINETTE 35**, follow the instructions mentioned under, A missed pill.

→ Talk to your doctor if your stomach upset carries on or gets worse**.** He or she may recommend another form of contraception.

Missed a period – could you be pregnant?

Occasionally, you may miss a withdrawal bleed. This could mean that you are pregnant, but that is very unlikely if you have taken your pills correctly. Start your next strip at the normal time. If you think that you might have put yourself at risk of pregnancy (for example, by missing pills or taking other medicines), or if you miss a second bleed, you should do a pregnancy test. You can buy these from the chemist or get a free test at your doctors surgery. If you are pregnant, stop taking **GINETTE 35** and see your doctor.

Taking more than one pill should not cause harm

It is unlikely that taking more than one pill will do you any harm, but you may feel sick, vomit or bleed from the vagina. Even girls who have not yet started to menstruate but have accidentally taken this medicine may experience such bleeding. Talk to your doctor if you have any of these symptoms.

When you want to get pregnant

If you are planning a baby, it's best to use another method of contraception after stopping **GINETTE**

35 until you have had a proper period. Your doctor or midwife relies on the date of your last natural period to tell you when your baby is due. However, it will not cause you or the baby any harm if you get pregnant straight away.

Possible Side Effects

Like all medicines, **CPA+EE** can cause side effects, although not everybody gets them. If you get any side effect, particularly if severe and persistent, or have any change to your health that you think may be due to **CPA+EE**, please talk to your doctor.

An increased risk of blood clots in your veins (venous thromboembolism (VTE)) or blood clots in your arteries (arterial thromboembolism (ATE)) is present for all women taking combined hormonal contraceptives.

The following is a list of the side effects that have been linked with the use of **CPA+EE**

Serious side effects – see a doctor straight away

Severe depression

Although, it is not considered a direct side effect of **CPA +EE,** some women have reported feeling depressed whilst taking **CPA +EE.** In very rare cases this has been associated with thoughts of ending their lives. If you develop severe depression, you should stop **CPA +EE** as a precaution, and see your doctor straight away.

Signs of a blood clot

- an unusual sudden cough;
- severe pain in the chest which may reach the left arm;
- breathlessness;
- any unusual, severe, or long-lasting headache or worsening of migraine;
- partial or complete loss of vision, or double vision;
- slurring or speech disability;
- sudden changes to your hearing, sense of smell, or taste;
- dizziness or fainting;
- weakness or numbness in any part of your body;
- severe pain in your abdomen;
- severe pain or swelling in either of your legs.

Signs of a severe allergic reaction or worsening of hereditary angioedema

- swelling of the hands, face, lips, mouth, tongue or throat.
- swollen tongue/throat may lead to difficulty swallowing and breathing
- a red bumpy rash (hives) and itching.

Signs of breast cancer include

- dimpling of the skin
- changes in the nipple
- any lumps you can see or feel.

Signs of cancer of the cervix include

- vaginal discharge that smells and/or contains blood
- unusual vaginal bleeding
- pelvic pain
- painful sex.

Signs of severe liver problems include

- severe pain in your stomach
- yellow skin or eyes (jaundice)
- inflammation of the liver (hepatitis)
- your whole body starts itching.

If you think you may have any of these, see a doctor straight away. You may need to stop taking **CPA+EE**.

Less serious side effects

Common side effects *(may affect up to 1 in 10 people)*

- feeling sick
- stomachache
- putting on weight
- headaches
- depressive moods or mood swings
- sore or painful breasts

Uncommon side effects *(may affect up to 1 in 100 people)*

- being sick and stomach upsets
- fluid retention
- migraine
- loss of interest in sex
- breast enlargement
- skin rash, which may be itchy

Rare side effects *(may affect up to 1 in 1,000 people)*

- poor tolerance of contact lenses
- losing weight
- increase of interest in sex
- vaginal or breast discharge
- venous blood clot

Tell your doctor or pharmacist if you are worried about any side effects which you think may be due to **CPA+EE**. Also tell them if any existing conditions get worse while you are taking **CPA+EE**.

Bleeding between periods should not last long

A few women have a little unexpected bleeding or spotting while they are taking **CPA +EE**, especially during the first few months. Normally, this bleeding is nothing to worry about and will stop after a day or two. Keep taking **CPA +EE** as usual. The problem should disappear after the first few strips.

You may also have unexpected bleeding if you are not taking your pills regularly, so try to take your pill at the same time every day. Also, unexpected bleeding can sometimes be caused by other medicines.

Make an appointment to see your doctor if you get breakthrough bleeding or spotting that:

- carries on for more than the first few months
- starts after you've been taking **CPA +EE** for a while
- carries on even after you've stopped taking **CPA +EE**.

Reporting of side effects

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779. By reporting side effects, you can help provide more information on the safety of this product.

Details of Manufacturer

Synokem Pharmaceuticals Ltd. Plot No.: 56-57, Sector-6A, I.I.E (SIDCUL), Ranipur (BHEL), Haridwar-249403 (Uttarakhand)

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Details of Permission or Licence Number with Date

M.L. 27/UA/SC/P-2018

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