

New Zealand Datasheet

1 PRODUCT NAME

GINET

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Cyproterone Acetate 2.00 mg and Ethinylestradiol Tablets 35 mcg.

3 PHARMACEUTICAL FORM

Each blister tray contains 21 yellow active tablets and 7 larger white inactive tablets. Each active tablet is a yellow, biconvex, film-coated tablet, containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms (0.035 mg) with a diameter of 5.7 mm. Each inactive tablet is a white, round, biconvex, tablet, plain on both sides with a diameter of 7.1 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Androgen-dependent diseases in women are an indication for treatment with GINET. These diseases may include: acne (where local treatment or oral antibiotics alone have not been successful), especially pronounced forms of acne that may be accompanied by inflammation or formation of nodes (acne nodulocystica, acne papulopustulosa), seborrhea, mild forms of hirsutism and/or androgenic alopecia.

Oral contraception in women requiring treatment for these androgen-dependent diseases is an indication for treatment with GINET. However, GINET is not recommended in women solely for contraception. It should not be used in combination with other hormonal contraceptives.

GINET is indicated for the relief of symptoms of polycystic ovary syndrome.

4.2 Dose and method of administration

Any previously used hormonal contraception should be discontinued. To achieve therapeutic efficacy and the required contraceptive protection, GINET needs to be taken regularly. The dose regimen of GINET is similar to the usual regimen for most combined oral contraceptives. Thus, the same administration rules for most combined oral contraceptives (COC's) must be considered.

Intermenstrual bleeding and eventual deterioration of the therapeutic and contraceptive reliability may be caused by not taking GINET regularly at about the same time each day.

How to take GINET

Tablets must be taken in the order directed on the blister each day at about the same time with some liquid as needed. Each subsequent blister is started after a 7-day period of non-hormonal (white or inactive) tablets, during which, withdrawal bleeding usually occurs. Usually 2 to 3 days after the last tablet the bleeding starts and may not have finished before the next blister is started. One hormonal (yellow or active) tablet is to be taken daily for 21 consecutive days.

How to start GINET

Where no preceding hormonal contraceptive use has occurred (in the previous month) GINET should be started on the first day of bleeding, taking the tablet in the red section marked with the appropriate day of the week. As an example, if bleeding starts on Monday then take the tablet in the red section of the blister marked "MON" for Monday.

One small yellow hormonal tablet is to be taken daily for 21 consecutive days. The white non-hormonal tablets are then taken daily for 7 days. Withdrawal bleeding should usually occur within 2 to 4 days after taking the last small yellow hormonal tablet.

In the first cycle only, an additional form of barrier method contraception must be used for the first 14 days of tablet taking. (Do not use rhythm or temperature methods as a contraceptive measure). Tablets should be taken at the same time each day.

Changing from another combined oral contraceptive (COC)

Start GINET in the red section of the blister on the day after the last hormonal tablet of her previous COC.

Changing from a progestogen only method (minipill, injection, implant)

The woman may switch from the minipill (or from an injectable when the next injection would be due, or from an implant on the day of its removal) to GINET immediately, but should be advised in all cases to use additional barrier method contraception for the first 14 days of tablet taking.

Following first trimester abortion

The woman may start immediately and needs to take additional contraceptive measures for the first 14 days of tablet taking.

Following delivery or second trimester abortion

Start taking tablets at day 21 to 28 after delivery or second trimester abortion. When starting later, additional contraception (barrier methods) should be used for the first 14 days of tablet taking. If intercourse has already occurred, pregnancy should be excluded first before the actual start of GINET use, or the woman should wait for her first menstrual period before starting GINET.

Extra Contraceptive Precautions

When you need extra contraceptive precautions, either:

Do not have sex; or

Use barrier contraceptive methods such as:

- Use a condom or;
- Use a cap plus spermicide.

Oral contraceptives can alter the usual menstrual cycle causing alterations in temperature and cervical mucus. Do not use the rhythm, or temperature methods as these will not be reliable.

Management of Missed Tablets (yellow hormonal tablets)

Missed tablets while taking the non-hormonal (white) tablets contained in GINET can be ignored, however they should be discarded.

Less than 12 hours late:

The woman will still have contraceptive protection if the tablet is taken less than 12 hours late. The tablet should be taken as soon as it is remembered, and further tablets should be taken at the usual time. Additional contraception or emergency contraception should not be required.

More than 12 hours late:

The woman may have reduced contraceptive protection if the tablet is taken more than 12 hours late. If tablets are missed at the beginning or end of the week of inactive tablets, there is a particularly high risk of pregnancy. If tablets are missed in the first week of taking active

tablets and intercourse took place in the preceding 7 days, then the possibility of pregnancy should be considered.

The following rules will aid in management of missed pills (these rules form the basis of the instructions to patients provided in the package insert):

- Tablet taking must never be discontinued for longer than 7 days.
- The 7 day rule: To maintain adequate suppression of the hypothalamic-pituitary-ovarian axis requires 7 days of uninterrupted tablet taking.
- Always continue taking your tablets at about the same time each day.

Before regaining contraceptive protection from pregnancy, you will need to take your small yellow hormonal tablet daily for the next 7 days in a row.

For the next 7 days while taking the next 7 small yellow hormonal tablets, use an additional contraception barrier method, such as condoms, or refrain from sexual intercourse.

If there are less than 7 small yellow hormonal tablets left in the current blister pack, finish the small yellow hormonal tablets and go straight on to the small yellow hormonal tablets of the next blister pack. This means that you miss out the white non-hormonal tablets if you have the 28-day pack. You may not have a period until the end of the next pack. This is not harmful.

If tablets have been missed and there is no withdrawal bleed in the first normal placebo-taking, then pregnancy should be considered.

Additionally

If tablets are missed in week 1 (Days 1 to 7) – due to the tablet free interval being extended, and if the woman has had unprotected sex in the tablet free interval or in week 1, then emergency contraception should be considered

If tablets are missed in week 3 (Days 15 to 21) - to avoid extending the tablet free interval, then the woman should finish the tablets in their current pack and start a new blister calendar pack the next day, thus omitting the tablet free tablet interval.

Advice in Case of Vomiting

Absorption may not be complete if vomiting occurs within 3-4 hours after tablet taking or if severe gastrointestinal disturbances occur. Additional contraceptive measures should be taken. The advice concerning missed tablets should be followed. After vomiting has occurred within 3 to 4 hours of taking a tablet; if the woman does not wish to change her normal tablet taking schedule, then an extra tablet(s) may be required from another blister pack.

How to Shift Periods or how to Delay a Period

If the woman wants to shift her periods to another day of the week than she is used to with her current scheme, she can omit the non-hormonal tablets in GINET by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough bleeding and spotting during the second pack.

Continuing with small yellow hormonal tablets from another blister pack of GINET without a tablet-free interval or the white non-hormonal tablets will allow a woman to delay a period. The extension can be continued for as long as desired until the end of the second blister pack. During the extension the woman may experience breakthrough bleeding or spotting.

Length of Use

As GINET is not recommended in women solely for contraception, in general, treatment should be continued over several months. The length of use depends on the severity of the treated condition and the patient's response. It is recommended to take GINET for at least another 3 to 4 cycles after the signs have subsided. Should there be a recurrence of the treated condition weeks or months after discontinuation of GINET, treatment should be resumed. A longer period of treatment may be recommended for the symptomatic relief of polycystic ovary syndrome. The need to continue treatment should be evaluated periodically by the treating doctor.

4.3 Contraindications

Oestrogen/progestogen preparations should not be used in the presence of any of the conditions listed below, and should be stopped immediately if any of the following conditions appear for the first time during use.

- Presence or a history of a cerebrovascular accident or venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction)
- Presence or history of prodromi for a thrombosis (e.g. angina pectoris, transient ischaemic attack)
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication
- Diabetes mellitus with vascular involvement
- History of epilepsy
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the breasts or the genital organs)
- History of migraine with focal neurological symptoms
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Pancreatitis or a history of pancreatitis if associated with severe hypertriglyceridemia
- Undiagnosed vaginal bleeding
- Hypersensitivity to any of the ingredients of GINET
- Concomitant use with another hormonal contraceptive
- Known or suspected pregnancy
- Lactation
- Meningioma or a history of meningioma

GINET is contraindicated for use with the Hepatitis C combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin (see section 4.4).

GINET is NOT to be used in men.

4.4 Special warnings and precautions for use

The benefits of the use of GINET should be weighed against the possible risks discussed below for each individual woman, and discussed with the woman before she decides to start using this medication. The woman should contact her doctor at the first appearance of any of these conditions or risk factors, or if these factors were already present and have been aggravated or exacerbated on use of GINET. The doctor then needs to decide whether its use should be discontinued.

Ginet is composed of the progesterone cyproterone acetate and the oestrogen ethinyloestradiol and is administered for 21 days of a monthly cycle. It has similar composition to that of a combined oral contraceptive.

Oestrogen/progestogen combinations like GINET have clinical and epidemiological information predominantly based on combined oral contraceptives (COCs).

Therefore, warnings related to the use of COCs apply also for GINET.

Circulatory Disorders

An increased risk of venous and arterial thrombotic and thromboembolic diseases such as stroke, myocardial infarction, pulmonary thrombosis, and deep venous embolism have been associated with the use of COCs, according to epidemiology research. These events occur rarely.

During the use of all COCs, pulmonary embolism and/or deep venous thrombosis may manifest due to venous thromboembolism (VTE). During the first year of COC use, the risk of venous thromboembolism is highest. VTE may be life threatening or, in 1-2% of cases, be fatal.

While there is no consensus as to whether these events are associated with the use of COCs and are extremely rare in COC users, thrombosis has been reported to occur in other blood vessels (e.g. mesenteric, hepatic, retinal arteries and veins or renal).

The approximate incidence of VTE for non-COC users is 4.4 per 10,000 woman years. This compares against COC users of low oestrogen doses (less than 50 mcg EE) of 8 to 10 per 10,000 woman years. This is substantially less than the incidence associated with pregnancy (i.e. 20 to 30 per 10,000 pregnant woman years).

Symptoms of arterial or venous thrombotic/thromboembolic events or of a cardiovascular accident can include: unilateral leg pain and/or swelling; pain or tenderness in the leg which may be felt only when standing or walking; increased warmth in the affected leg; red or discoloured skin on the leg; sudden severe chest pain, which may increase with deep breathing, pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; rapid or irregular heartbeat; any unusual, severe, prolonged headache; sudden breathlessness; sudden onset of coughing; collapse with or without focal seizure; diplopia; sudden partial or complete loss of vision; slurred speech or aphasia; weakness or very marked numbness suddenly affecting one side or one part of the body; vertigo; 'acute' abdomen; motor disturbances; fullness, indigestion or choking feeling; sweating; nausea; vomiting.

Some of these symptoms (e.g. "shortness of breath", "coughing") are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Arterial thromboembolic events may be life threatening or have a fatal outcome.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors, or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. GINET should not be prescribed in women with a negative benefit assessment (see section 4.3).

Factors increasing the risk of cerebrovascular accident and or venous and/or arterial thromboembolism include:

- Smoking (especially in women over 35 years of age; heavier smoking and increasing age further increases the risk)
- Age

- A positive family history (i.e. venous or arterial thromboembolism event in a sibling or parent at a relatively early age). The woman should be referred to a specialist for advice before deciding about any COC if a hereditary predisposition is suspected.
- Obesity (body mass index over 30 kg/m²)
- Hypertension
- Dyslipoproteinaemia
- Valvular heart disease
- Migraine
- Atrial fibrillation
- Prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. It is advisable to discontinue COC use in these situations, (at least four weeks in advance in the case of elective surgery) use should not resume until two weeks after complete mobilization.

Varicose veins and superficial thrombophlebitis may or may not have an effect on venous thromboembolism. The increased risk of thromboembolism in the puerperium must be considered.

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

Other medical conditions, which have been associated with adverse circulatory events include: polycystic ovary syndrome (the beneficial effects of GINET on polycystic ovary syndrome may offset the suggested increased risk of adverse circulatory effects), diabetes mellitus, haemolytic uraemic syndrome, systemic lupus erythematosus, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell anaemia.

There are some biochemical factors that may indicate a hereditary or acquired predisposition for venous or arterial thrombosis. These include: Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

The doctor 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 use, when assessing the risk/benefit of using GINET. In case of a restart of GINET (following a 4 week or greater pill interval), the increased risk of VTE should be considered.

Tumours

There is a slightly increased relative risk (RR = 1.24) of diagnosing breast cancer in women who are currently using COCs. This was reported in a meta-analysis from 54 epidemiological studies. During the course of ten years post cessation of COC, the risk of diagnosing breast cancer gradually disappears. The excess number of breast cancer diagnoses in current and recent COC users is small compared to the risk of breast cancer overall as breast cancer is rare in women under 40 years of age. COC use in studies has not been identified as evidence for breast cancer. Earlier breast cancer diagnosis in COC users, the biological effects of COCs or a combination of both may contribute to the observed pattern of increased risk. Users of COC tend to have less clinically advanced breast cancer upon diagnosis than that diagnosed in non-users.

Some epidemiological studies have indicated that the development of cervical cancer may be contributed to by long-term use of COCs (the single most important risk factor for development is the persistent infection with human papilloma virus), however there is continuing controversy regarding the extent to which this finding is attributable to the

confounding effects (e.g. cervical screening and sexual behaviour including use of barrier contraceptives).

A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs. In COC users, rarely, benign, and even more rarely, malignant liver tumours have been reported. These tumours have led to life-threatening intra-abdominal haemorrhages in isolated cases.

Meningiomas: The occurrence of (multiple) meningiomas has been reported in association with longer term use (years) of cyproterone acetate at doses of 25 mg/day and above. This is twelve and half times the normal daily dosage of cyproterone at 2mg per active tablet per day in GINET. If a patient treated with GINET is diagnosed with meningioma, treatment with GINET must be stopped.

Malignancies may be life threatening or have a fatal outcome.

Other Precautions

Each yellow tablet contains 36.77 mg of lactose and each white placebo tablet contains 84.357 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose free diet should take this amount into consideration.

Hypertension:

Many women taking COCs have had small increases in blood pressure reported, however clinically relevant increases are rare. The doctor should advise withdrawal of the COC if a sustained clinically significant hypertension develops during the COC use and the hypertension should be treated. If normotensive values can be achieved with antihypertensive therapy, COC use may be resumed if considered appropriate by the doctor.

Hypertriglyceridemia and pancreatitis:

Women using COCs may be at risk of pancreatitis if they have hypertriglyceridemia, or a family history of hypertriglyceridemia.

Pregnancy:

Jaundice and/or pruritus related to gallstone formation; cholestasis; systemic lupus erythematosus; porphyria; Sydenham's chorea; haemolytic uraemic syndrome; herpes gestationis; otosclerosis-related hearing loss have been reported to occur or deteriorate with both pregnancy and COC use. The evidence of an association with COC use is inconclusive. If cholestatic jaundice that initially occurred during pregnancy or previous use of sex steroids reoccurs, COC use should be ceased.

Administration of GINET is contraindicated in pregnancy.

If pregnancy occurs during treatment with GINET, use is to be stopped immediately.

Liver function:

Disturbances of liver function (acute or chronic) may indicate COC use discontinuation until liver function returns to normal (as assessed via liver function markers). Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Diabetes:

Diabetic women should be carefully monitored while taking COCs as COCs may have an effect on peripheral insulin resistance and glucose tolerance. However, there is no evidence for a need to alter the therapeutic regimen in diabetes using COCs.

Bleeding Irregularities:

Withdrawal bleeding may not occur during the interval where the white inactive pills are being taken, or during the tablet free interval, in some women. It is unlikely that the woman is pregnant if the suggested directions for taking the COC have been followed. If two withdrawal bleeds are missed or if the COC has not been taken according to these directions prior to the first missed withdrawal bleeding, pregnancy must be ruled out before COC use is continued.

Irregular bleeding may occur with oestrogen/progestogen combinations, especially during the initial months of use. After an adapting period of three cycles, the evaluation of an irregular bleeding becomes more meaningful. Persistent irregular bleeding, or a period of irregular bleeding after previously regular cycles indicates that the bleeding may be unrelated to hormones, diagnostic measures should be taken to rule out malignancy or pregnancy. These may include curettage.

Crohn's disease:

Has been associated with COC use.

Ulcerative colitis:

Has been associated with COC use.

Chloasma:

Women should avoid exposure to the sun or ultraviolet radiation whilst taking COCs if they have a tendency to chloasma. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum.

Hirsutism:

If symptoms have recently developed or increased substantially in women suffering from hirsutism, the causes (androgen-producing tumor, adrenal enzyme defect) must be clarified by differential diagnosis.

Hepatitis C:

During clinical trials with the combination drug regimen ombitasvir / paritaprevir / ritonavir and dasabuvir with and without ribavirin, transient, asymptomatic elevations of alanine transaminase (ALT) greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinyloestradiol-containing medications such as combined oral contraceptives, contraceptive patches, or contraceptive vaginal rings.

GINET must be discontinued 2 weeks prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin. GINET can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

Medical Examination

complete medical history and physical examination should take place prior to the initiation or reinstatement of GINET, with a focus on the contraindications and warnings.

Contraindications (e.g. a transient ischaemic attack) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of GINET, therefore periodic medical assessment is important. The clinical exam should be complete and thorough, with a particular emphasis on blood pressure, breasts, abdomen and pelvic

organs, including cervical cytology, and relevant laboratory tests. The frequency and nature of these periodic examinations need to be adapted to the individual.

GINET does NOT protect women from sexually transmitted diseases or HIV (AIDS) and women should be advised of this.

Reduced Efficacy

Missed tablets, vomiting or certain medications may reduce the efficacy of GINET.

4.5 Interaction with other medicines and other forms of interaction

Using oestrogen/progestogen combinations like GINET in combination with other drugs may lead to interaction between the drugs and breakthrough bleeding and/or contraceptive failure may occur.

The following interactions have been reported in the literature.

Hepatic metabolism

Increased clearance of sex hormones can arise when interactions occur with medicines that induce microsomal enzymes. This has been established for phenytoin, barbiturates, primidone, carbamazepine, rifabutin, rifampicin, oxcarbamazepine, topiramate, felbamate, fitonavir, griseofulvin and products containing St John's Wort.

It has been reported that potentially hepatic metabolism has been affected in combination or alone with non-nucleoside reverse transcriptase (e.g. nevirapine) and HIV protease inhibitors (e.g. ritonavir).

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the oestrogen or the progestogen or both.

Women being treated with any of these medicines should use a temporary barrier method in addition to GINET, or choose another method of contraception. With microsomal enzyme-inducing medicines, the barrier method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the hormone-containing yellow coated tablets in the GINET pack, the hormone-free white tablets should be omitted and the next pack be started.

Interference with enterohepatic circulation

When certain antibiotic agents are given (e.g. penicillins, tetracyclines), according to some reports, ethinylestradiol concentrations may be reduced due to a decreased entero-hepatic circulation of estrogens. Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method or another method of contraception until 7 days after discontinuation.

For women taking rifampicin and griseofulvin with GINET, the barrier method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation.

If the period during which the additional contraceptive protection using barrier methods includes the white inactive tablets, they should not be taken and the next blister pack started using active small yellow hormonal tablets without delay.

Plasma and tissue concentrations of other drugs may be altered as oestrogen/progestogen combinations like GINET may interfere with the metabolism of other medicines. Increased metabolism can occur (e.g. cyclosporin) or decreased metabolism can occur (e.g. lamotrigine).

Laboratory Tests

Certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins (e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of coagulation and fibrinolysis and parameters of carbohydrate metabolism) can be influenced by the use of preparations like GINET. The changes are generally within the normal laboratory range.

Exogenous oestrogens may induce or exacerbate symptoms of angioedema in patients with hereditary angiodema.

4.6 Fertility, pregnancy and lactation

Embryotoxicity/Teratogenicity

Embryotoxic or teratogenic effects have been investigated using the active ingredients in combination. Administration during organogenesis and before development of the external genitalia gave no indication of a general teratogenic effect. Signs of feminisation in male foetuses could occur following higher doses of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs (after day 45 of gestation). There were no signs of feminization in male newborn children who had been exposed *in utero* to cyproterone acetate.

Pregnancy

GINET use is contraindicated in pregnancy. If pregnancy occurs during treatment with GINET, use should be immediately stopped.

Lactation

Lactation is a contraindication for GINET administration. Cyproterone acetate is transferred into the milk of lactating women. Newborns will receive an approximate dose of 1mcg/kg in the milk as around 0.2% of the maternal dose is transferred. Newborns via milk could receive 0.02% of the daily maternal dose of ethinylestradiol during established lactation.

4.7 Effects on ability to drive and use machines

No negative effects have been observed.

4.8 Undesirable effects

See the sections 4.3 and 4.4 for the most serious risks associated with use of GINET. Other side effects that have been reported, but the association has been neither established nor disproven, are listed below.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$) and rare ($\geq 1/10,000$ and $< 1/1000$)

Eye disorders

Rare: Contact lens intolerance

Gastrointestinal disorders

Common: Nausea, Abdominal pain

Uncommon: Vomiting, Diarrhoea

Immune system disorders

Rare: Hypersensitivity

Investigations

Common: Increased weight

Rare: Decreased weight

Metabolism and nutrition disorders

Uncommon: Fluid retention

Nervous system disorders

Common: Headache

Uncommon: Migraine

Psychiatric disorders

Common: Depressed mood, Altered mood

Uncommon: Decreased libido

Rare: Increased libido

Reproductive system and breast disorders

Common: Breast pain, Breast tenderness

Uncommon: Breast hypertrophy

Rare: Vaginal discharge, Breast discharge

Skin and subcutaneous tissue disorders

Uncommon: Rash, Urticaria

Rare: Erythema nodosum, Erythema multiforme

Vascular Disorders

Rare: Thromboembolism

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

There have been no reports of serious deleterious effects from overdose.

Symptoms

Symptoms that may occur in this case are vomiting, nausea, and in young girls, slight vaginal bleeding.

Treatment

There are no antidotes and further treatment should be symptomatic.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code G03HB01

The sebaceous gland and hair follicle together make up the pilosebaceous unit. This pilosebaceous unit is an androgen-sensitive component of skin. Changes to the skin, can result in the following clinical conditions; acne, seborrhoea, hirsutism and androgenic alopecia. Higher plasma levels of androgen or increased sensitivity to androgen may cause these clinical conditions.

The active ingredients, cyproterone acetate and ethinylestradiol in GINET both beneficially influence the hyper-androgenic disease state. Cyproterone acetate inhibits the synthesis of androgen by the target cell, as it is a competitive antagonist on the androgen receptor, and it has an anti-gonadotropic effect therefore decreasing androgen blood concentrations. Ethinylestradiol up-regulates the synthesis of Sex-Hormone-Binding-Globulin (SHBG) in plasma which reduces the amount of free, biologically available androgen in the bloodstream, which amplifies the anti-gonadotropic effect of cyproterone acetate.

Usually, after three to four months of therapy using GINET, existing acne efflorescences are treated. Excessive hair and skin greasiness due to seborrhea will usually resolve prior to the acne. Alopecia (hair loss), if experienced, also decreases as the seborrhea resolves. Resolution of mild hirsutism (particularly slightly increased facial hair) becomes apparent only after several months of treatment.

The contraceptive effect of GINET includes the inhibition of ovulation and changes in the cervical secretion. While these are the most important factors, there are various other dynamics involved. Oestrogen/progesterone combinations cause the menstrual cycle to be more regular, and menstruation to be less painful with lighter bleeding. GINET is not recommended for contraception alone.

Combined oral contraceptives at higher doses (containing 50mcg of ethinylestradiol) may reduce the risk of fibrocystic breast tumours, endometrial and ovarian cancer, ovarian cysts, ectopic pregnancy and pelvic inflammatory disease. This may also be true for lower doses of combined oral contraceptives (COCs).

5.2 Pharmacokinetic properties

Cyproterone acetate

Absorption

Cyproterone acetate (CPA) is completely absorbed in a wide dose range following oral administration. After taking a tablet, at 1.6 hours post ingestion, peak serum concentrations of 15ng/mL are reached. CPA is approximately 88% bioavailable.

Distribution

A very high proportion of CPA is exclusively bound to serum albumin. The free steroid concentration in serum makes up 3.5% to 4.0% of the total serum concentration. The serum binding of CPA is not affected by the ethinylestradiol-induced increase in SHBG. The apparent volume of distribution is about 986L ± 437 L.

Metabolism

CPA is almost completely metabolised. The clearance rate from serum is about 3.6 mL/min/kg. 15β-OH-CPA was the main metabolite identified in plasma, which is formed via the cytochrome P450 enzyme CYP3A4.

Elimination

There are two phases of decreasing CPA serum levels, which have half-lives of 0.8 hours and approximately 2.3 to 3.3 days. CPA metabolites are excreted at a urinary to biliary ratio

of about 1:2, the half-life of the metabolite excretion is about 1.8 days. Some CPA is excreted unchanged.

Steady state conditions

CPA pharmacokinetics is not affected by SHBG levels. A steady-state condition of about 2.5 fold serum concentration is reached in the second half of the treatment cycle, following daily ingestion.

Ethinylestradiol

Absorption

Ethinylestradiol (EE) is rapidly and completely absorbed after oral administration. After taking a tablet at 1.6 hours post ingestion, a peak serum concentration of approximately 71 pg/mL is reached. EE has a mean oral bioavailability of about 45% after being extensively metabolised during absorption and first-liver passage. There is an inter-individual variation of about 20% to 65%.

Distribution

Approximately 98% of EE is highly but non-specifically bound to serum albumin. An apparent volume of distribution of about 2.8 to 8.6 L/kg was determined; ethinylestradiol induces an increase in the serum concentrations of SHBG.

Metabolism

Pre-systemic conjugation of EE occurs in both the small bowel mucosa and the liver. EE is mainly metabolised by aromatic hydroxylation, however, a wide variety of metabolites are formed by hydroxylation and methylation methods. These conjugate with glucuronides and sulphate, as well as existing as free metabolites. The clearance rate was reported to be approximately 2.3 - 7 mL/min/kg.

Elimination

There are two dispositional phases of diminishing EE serum levels, which have half-lives of about 1 hour and 10 to 20 hours. EE metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of the metabolite excretion is about 1 day. Unchanged EE is not excreted.

Steady-state conditions

Compared with a single dose, steady steady-state conditions are reached when serum levels are increased by 60% during the second half of a treatment cycle.

5.3 Preclinical safety data

There is no relevant preclinical data on ethinylestradiol that will provide additional safety information that is not already included in other sections. The ethinylestradiol toxicity profile is well known.

There is no specific risk for humans based on repeated dose toxicity of cyproterone acetate in conventional studies. The possible sensitising effect of ethinylestradiol and cyproterone acetate has not been investigated in animal-experimental studies.

Genotoxicity and Carcinogenicity

Recognised genotoxicity first-line tests with cyproterone acetate gave negative results. While DNA-adduct levels in dog liver cells was extremely low, cyproterone acetate has been shown to be capable of producing adducts with DNA (and an increase in DNA repair activity) in liver cells from rats and monkeys and also in freshly isolated human hepatocytes. This DNA-adduct formation occurred at levels that might be expected to occur at the recommended dose for treatment with cyproterone acetate. Female rats treated with cyproterone acetate had an increased incidence of possibly pre-neoplastic, focal liver lesions

where cellular enzymes were altered. In transgenic rats carrying a bacterial target gene for mutation, there was an increase in mutation frequency. Investigations into the tumourigenicity of cyproterone acetate in rodents did not indicate a specific tumourigenic potential.

An increased incidence of hepatic tumours in man is not supported by the current clinical experience and epidemiological trials to date. However, sexual steroids can promote the growth of certain hormone-dependent tissues and tumours that are already present.

Generally, if used as directed, for the given indications, and at the recommended dose, according to the data available from research, cyproterone acetate and ethinylestradiol specifically in combination as a contraceptive should not raise any concerns for use in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The white inactive tablets contain as excipients: lactose, starch, microcrystalline cellulose, talc, magnesium stearate, colloidal anhydrous silica, hypromellose, titanium dioxide and propylene glycol.

The yellow active tablets contain as excipients: lactose, povidone, starch, talc, magnesium stearate, hypromellose, titanium dioxide, quinoline yellow, propylene glycol.

6.2 Incompatibilities

None known.

6.3 Shelf life

Shelf life is 36 months (3 years) from manufacture.

6.4 Special precautions for storage

Store below 25°C.

Store out of reach of children.

GINET tablets should not be used after the expiry date (EXP) which is stated on the pack. The expiry date refers to the last day of that month.

GINET tablets do not contain gluten.

6.5 Nature and contents of container

Six PVC/aluminium blister trays of 28 tablets.

6.6 Special precautions for disposal

No special requirements

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

REX Medical Limited
PO Box 18-119
Glen Innes

Auckland 1743

Telephone: (09) 574 6060

Fax: (09) 574 6070

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10 DATE OF REVISION OF THE TEXT

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.3	Meningioma or a history of meningioma
4.4	Additional information on meningiomas