

New Zealand Datasheet

Name of Medicine

GINET-63

GINET-84

Cyproterone Acetate/Ethinylestradiol Tablets

Presentation

GINET-63: Each blister tray contains 21 yellow biconvex, film-coated active tablets. Each tablet contains cyproterone acetate 2 mg and ethinylestradiol 35 micrograms (0.035 mg) with a diameter of 5.7 mm.

GINET-84: 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.

Uses

Actions

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-63 or GINET-84 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-63 or GINET-84, 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-63 or GINET-84 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-63 or GINET-84 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).

With higher-dosed combined oral contraceptives (COCs) which contain ethinylestradiol 50 mcg, there is evidence of a reduced risk of fibrocystic breast tumours, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer which may also apply to lower dosed COCs.

Pharmacokinetics

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 70 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.

Indications

Androgen-dependent diseases in women are an indication for treatment with GINET-63 or GINET-84. 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-63 or GINET-84. However GINET-63 or GINET-84, is not recommended in women solely for contraception.

GINET-63 or GINET-84 is indicated for the relief of symptoms of polycystic ovary syndrome.

Dosage and Administration

Any previously used hormonal contraception should be discontinued. To achieve therapeutic efficacy and the required contraceptive protection, GINET-63 or GINET-84 needs to be taken regularly. The dose regimen of GINET-63 or GINET-84 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-63 or GINET-84 regularly at about the same time each day.

How to take GINET-63 or GINET-84

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 (GINET-84) or a 7-day tablet free interval (GINET-63), 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 (GINET-63 or GINET-84).

GINET-63

How to start GINET-63

No previous hormonal contraceptive use

If there has been no previous hormonal contraceptive use (in the previous month), the first tablet of GINET-63 must be taken preferably on the first day of the cycle (first day of bleeding). During the first cycle, an additional non-hormonal contraceptive barrier method (using condoms, or cap and spermicide), is recommended for the first 7 days of yellow hormonal tablet taking, especially if starting on day 2 to 5. The rhythm or temperature contraceptive method is NOT recommended.

Changing from another combined oral contraceptive (COC)

The woman should start with GINET-63 preferably on the day after the hormonal (or active) tablet of her previous combined oral contraceptive (COC), but at latest on the day following the usual tablet free or non-hormonal tablet interval of her previous COC.

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

The woman may change any day from the minipill (or from an injectable when the next injection would be due, or from an implant on the day of its removal) but should in all cases be advised to use additional contraception (barrier methods) for the first 7 days of tablet taking.

Following first trimester abortion

The woman may start immediately. Upon doing so, the woman need not take additional contraceptive measures.

Following delivery or second trimester abortion

After delivery or second trimester abortion, women should be advised to start at day 21 to 28. However, when starting later than that, the woman should be advised to use additional contraception (barrier methods) for the first 7 days of tablet taking. If intercourse has already occurred, pregnancy should be excluded before the actual start of GINET-63 or the woman has to wait for her first menstrual period.

GINET-84

How to start GINET-84

Where no preceding hormonal contraceptive use has occurred (in the previous month) GINET-84 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-84 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-84 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 need not take additional contraceptive measures.

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-84 use, or the woman should wait for her first menstrual period before starting GINET-84.

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-84 can be ignored.

Less than 12 hours late:

The woman will still have contraceptive protection if the tablet is 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 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-84 by as many days as she likes or shorten her upcoming tablet-free interval with GINET-64. 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-63 or GINET-84 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-63 or GINET-84, 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-63 or GINET-84 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-63 or GINET-84, treatment should be resumed. A longer period of treatment may be recommended for the symptomatic relief of polycystic ovary syndrome.

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-63 or GINET-84
- Known or suspected pregnancy
- Lactation

GINET-63 and GINET-84 is NOT to be used in men.

Warnings and Precautions

The benefits of the use of GINET-63 and GINET-84 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-63 and GINET-84. The doctor then needs to decide whether its use should be discontinued.

Oestrogen/progestogen combinations like GINET-63 and GINET-84 have clinical and epidemiological information predominantly based on combined oral contraceptives (COCs).

Therefore, warnings related to the use of COCs apply also for GINET-63 and GINET-84.

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.

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 0.5 to 3 per 10,000 woman years. This compares against COC users of low oestrogen doses (less than 50 mcg EE) of up to 4 per 10,000 woman years. This compares against the incidence of VTE occurring during COC use which is substantially less than the incidence associated with pregnancy (i.e. 6 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; sudden severe chest pain, which may or may not radiate to the left arm; 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.

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-63 and GINET-84 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-63 and GINET-84.

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 lead to life-threatening intra-abdominal haemorrhages in isolated cases.

Other Precautions

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-63 or GINET-84 is contraindicated in pregnancy.

If pregnancy occurs during treatment with GINET-63 or GINET-84, 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).

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.

Medical Examination

A complete medical history and physical examination should take place prior to the initiation or reinstatement of GINET-63 or GINET-84, 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-63 or GINET-84, 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-63 and GINET-84 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-63 or GINET-84.

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 is a contraindication for the use of GINET-63 or GINET-84.

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 objections for usage in humans.

Use in Pregnancy

GINET-63 and GINET-84 use is contraindicated in pregnancy. If pregnancy occurs during treatment with GINET-63 or GINET-84, use should be immediately stopped.

Use in Lactation:

Lactation is a contraindication for GINET-63 or GINET-84 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.

Effects on Ability to Drive or Operate Machinery

No negative effects have been observed.

Adverse Effects

See the contraindications and warning section for the most serious risks associated with use of GINET-63 and GINET-84. Other side effects that have been reported, but the association has been neither confirmed nor refuted are listed below

Common ($\geq 1/100$)

Nausea, headaches, abdominal pain, weight gain, depressed or altered mood, breast pain or tenderness.

Uncommon ($\geq 1/1000$ and $<1/100$)

Vomiting, migraine, diarrhoea, fluid retention, breast hypertrophy, decrease in libido, rash or urticaria.

Rare (<1/1000)

Contact lens intolerance, increase in libido, weight loss, hypersensitivity, vaginal or breast discharge erythema nodosum or erythema multiforme, thromboembolic events.

Interactions

Using oestrogen/progestogen combinations like GINET-63 and GINET-84 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, fitoronavir, griseofulvin and products containing St John's Wort.

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

Women being treated with any of these medicines should use a temporary barrier method in addition to GINET-63 or GINET-84, 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.

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-63 or GINET-84, 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-63 and GINET-84 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-63 or GINET-84. The changes are generally within the normal laboratory range.

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

Overdosage

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.

Pharmaceutical Precautions

Store below 25°C.

Store out of reach of children.

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

Medicine Classification

Prescription Medicine.

Package Quantities

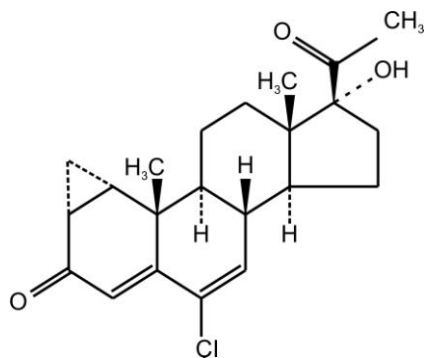
GINET-63: Three blister trays of 21 tablets.

GINET-84: Three blister trays of 28 tablets.

Further Information

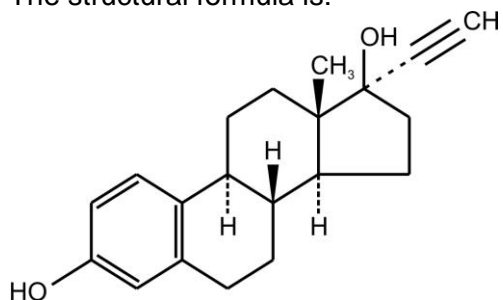
The chemical name of cyproterone acetate is: (1 β ,2 β)-6-Chloro-1,2-dihydro-17-hydroxy-3'H-cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione acetate (C₂₄H₂₉ClO₄)

The structural formula is:



The chemical name of ethinylestradiol is: (17 α)-19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol (C₂₀H₂₄O₂).

The structural formula is:



Pre-Clinical 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.

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.

Name and Address

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Date of Preparation

16 November 2011