SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

ELOINE® PLUS
Film-coated tablets

COMPOSITION:

The 28-day pack (Every-Day pack) contains 24 hormone-containing pink film-coated tablets each with 3 mg drospirenone, 0,020 mg ethinylestradiol (as betadex clathrate) and 0,451 mg levomefolate calcium (equimolar to 0,400 mg folic acid), plus 4 hormone-free light orange film-coated tablets each with 0,451 mg levomefolate calcium.

Other excipients: croscarmellose Na, hydroxypropylcellulose, hypromellose , iron oxide red, iron oxide yellow, lactose monohydrate, macrogol 6000, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide.
Contains lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION:

A 21.8.2 Progesterones with estrogens

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

The contraceptive effect of combined oral contraceptives is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion.

Drospirenone exerts antiandrogenic activity.
Drospirenone is devoid of androgenic, estrogenic, glucocorticoid and antiglucocorticoid activity.

ELOINE PLUS is a combined oral contraceptive with ethinylestradiol, the progestogen drospirenone and the vitamin levomefolate calcium.

Levomefolate calcium is a stable salt of the naturally occurring form of folates and is the predominant folate form in foods. Prevention of folate deficiency is recommended even before the onset of pregnancy in order to achieve an adequate folate status early in pregnancy.

Pharmacokinetic properties:

- **Drospirenone**

Absorption:
Orally administered drospirenone is rapidly and almost completely absorbed. Peak serum concentrations of approximately 35 ng/ml are reached at about 1 to 2 hours after single ingestion. Bioavailability is about 76 to 85 %. Concomitant ingestion of food has no influence on bioavailability, but the maximum concentration was reduced in comparison to intake on an empty stomach.

Distribution:
After oral administration, serum drospirenone levels decrease in two phases which are characterised by half-lives of 1,6 ± 0,7 hours and 27,0 ± 7,5 hours, respectively. Drospirenone is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). Only 3 to 5 % of the total serum concentrations are present as free steroid. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of drospirenone. The mean apparent volume of distribution of drospirenone is 3,7 ± 1,2 l/kg.

Metabolism:
Drospirenone is extensively metabolised after oral administration. The major metabolites in the plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulphate, both of which are formed without involvement of the P450 system. Drospirenone is metabolised by cytochrome P450 3A4 and has demonstrated a capacity to inhibit this enzyme and cytochrome P450 1A1, cytochrome P450 2C9 and cytochrome P450 2C19 *in vitro*.

Elimination:
The metabolic clearance rate of drospirenone in serum is 1,5 ± 0,2 ml/min/kg. Drospirenone is excreted only in trace amounts in unchanged form. The metabolites of drospirenone are excreted with the faeces and urine at an excretion ratio of about 1,2 to 1,4. The half-life of metabolite excretion with the urine and faeces is about 40 hours.

Steady-state conditions:
During a treatment cycle, maximum steady-state concentrations of drospirenone in serum of about 60 ng/ml are reached between day 7 and day 14 of treatment. Serum drospirenone levels accumulated by a factor of about 3 as a consequence of the ratio of terminal half-life and dosing interval. Further accumulation of drospirenone levels beyond treatment cycles was observed between cycles 1 and 6 but thereafter, no further accumulation was observed.

Special populations:

Effect of renal impairment:
Steady-state serum drospirenone levels in women with mild renal impairment (creatinine clearance CLcr, 50 to 80 ml/minute) were comparable to those of women with normal renal function (CLcr, > 80 ml/minute). The serum drospirenone levels were on average 37 % higher in women with moderate renal impairment (CLcr, 30 to 50 ml/minute) compared to those in women with normal renal function. Drospirenone treatment was well tolerated by all groups. Drospirenone treatment did not show any clinically significant effect on serum potassium concentration. Severe renal impairment has not been studied.

Effect of hepatic impairment:
In women with moderate hepatic function, (Child-Pugh B) mean serum drospirenone concentration-time profiles were comparable to those of women with normal hepatic function during the absorption/distribution phases with similar C_{max} values. The mean terminal half-life of drospirenone for the volunteers with moderate hepatic impairment was 1,8 times greater than for the volunteers with normal hepatic function.
An about 50 % decrease in apparent oral clearance (CL/f) was seen in volunteers with moderate hepatic impairment as compared to those with normal liver function. The observed decline in drospirenone clearance in volunteers with moderate hepatic impairment compared to normal volunteers did not translate into any apparent difference in terms of serum potassium concentrations between the two groups of volunteers.

- **Ethinylestradiol**

Absorption:
Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 88 to 100 pg/ml are reached within 1 to 2 hours after single oral administration. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60 %. Concomitant intake of food reduced the bioavailability of ethinylestradiol in about 25 % of the investigated subjects while the maximum concentration was reduced in all subjects.

*Distribution**:***
Serum ethinylestradiol levels decrease in two phases; the terminal disposition phase is characterised by a half-life of approximately 24 hours. Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98,5 %) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5 l/kg was determined.

Metabolism:
Ethinylestradiol is subject to presystemic conjugation in both the small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates

with glucuronides and sulphate. The metabolic clearance rate of ethinylestradiol is about 5 ml/min/kg.

Elimination:
Ethinylestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinylestradiol are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions:
Steady-state conditions are reached during the second half of a treatment cycle and serum levels of ethinylestradiol accumulate by a factor of about 1,4 to 2,1.

- **Levomefolate calcium**

Absorption:
Orally administered levomefolate calcium is absorbed rapidly and is incorporated into the body folate pool. Peak plasma concentrations of about 50 nmol/l above baseline are reached within 0,5 to 1,5 hours after single oral administration of 0,451 mg levomefolate calcium.

Distribution:
Biphasic kinetics is reported for folates with a fast- and a slow-turnover pool. The fast-turnover pool probably reflecting newly absorbed folate is consistent with the terminal half-life of approximately 4 to 5 hours after single oral administration of 0,451 mg levomefolate calcium.
The slow-turnover pool reflecting turnover of folate polyglutamate has a mean residence time of greater than or equal to 100 days. Exogenous folate and an enterohepatic folate cycle help to maintain a constant supply of L-5-methyl-THF.

Elimination:
L-5-methyl-THF is eliminated from the body by urinary excretion of intact folates and catabolic products as well as faecal excretion through a biphasic kinetics process. A rapid decline in urinary and faecal concentration of folates and their catabolites with a half-life of several hours is followed by a long decline with a half-life of about 100 to 360 days.

Steady-state conditions:
Steady-state conditions for L-5-methyl-THF in plasma after intake of 0,451 mg levomefolate calcium are reached after about 8-16 weeks depending on the baseline levels. In red blood cells achievement of steady state is delayed due to the long life-span of red blood cells of about 120 days.

INDICATIONS:

- Oral contraception.
- Improvement in folate status in women who elect to use oral contraception.
- Treatment of moderate acne vulgaris in women seeking oral contraception.
- Treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who have chosen oral contraception as their method of birth control. The efficacy of ELOINE PLUS for PMDD was not assessed beyond 3 cycles. ELOINE PLUS has not been evaluated for treatment of premenstrual syndrome (PMS).

CONTRA-INDICATIONS:

ELOINE PLUS 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 treatment with ELOINE PLUS, the product should be stopped immediately.

- Hypersensitivity to the active substances or to any of the excipients of ELOINE PLUS.
- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident.
- Presence or history of prodromata of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis (see “Warnings”).

- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- Severe hepatic disease as long as liver function values have not returned to normal.
- Severe renal insufficiency or acute renal failure with a creatinine clearance of < 30 ml/min.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.

WARNINGS AND SPECIAL PRECAUTIONS:

Circulatory disorders:

Epidemiological studies have demonstrated an association between the use of combined oral contraceptives such as ELOINE PLUS and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents.

The risk of VTE is highest during the first year of use. This increased risk is present after initially starting ELOINE PLUS or restarting (following a 4 week or greater pill free interval) the same or a different combined oral contraceptive. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

Overall the risk for venous thromboembolism (VTE) in users of low estrogen dose combined oral contraceptives is two to threefold higher than for non-users of combined oral contraceptives who are not pregnant.

VTE may be life-threatening or may have a fatal outcome.

Venous thromboembolism, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur.

The occurrence of thrombosis has been reported in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in ELOINE PLUS users.

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

The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:

- age;
- smoking (with heavier smoking and increasing age the risk increases further, especially in women over 35 years of age);
- a positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any combined oral contraceptive use;
- obesity (body mass index over 30 kg/m^2);
- dyslipoproteinaemia;
- hypertension;
- migraine;
- valvular heart disease;
- atrial fibrillation;
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue combined oral contraceptive use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

The increased risk of thromboembolism in the puerperium must be considered (see “Pregnancy and lactation”).

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.

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

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

Tumours:

The most important risk factor for cervical cancer is persistent human papilloma virus infection. Some epidemiological studies have indicated that long-term use of ELOINE PLUS may further contribute to an increased risk of cervical 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 ELOINE PLUS. The excess risk gradually disappears during the course of the 10 years after cessation of ELOINE PLUS use.

Benign liver tumours and, malignant liver tumours have been reported in users of ELOINE PLUS. These tumours have led to life-threatening intraabdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intraabdominal haemorrhage occur in women taking ELOINE PLUS.

Other conditions:

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using combined oral contraceptives such as ELOINE PLUS.

Small increases in blood pressure have been reported in many women taking ELOINE PLUS, and clinically relevant increases may occur. If a sustained clinically significant hypertension develops during the use of ELOINE PLUS then it is prudent for the medical practitioner to withdraw ELOINE PLUS and treat the hypertension.

The occurrence or deterioration of the following conditions have been reported with ELOINE PLUS use: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham’s chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens such as contained in ELOINE PLUS may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of ELOINE PLUS. Recurrence of cholestatic jaundice which first occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of ELOINE PLUS.

ELOINE PLUS may have an effect on peripheral insulin resistance and glucose tolerance. Hence, diabetic women should be carefully observed while taking ELOINE PLUS.

Crohn’s disease and ulcerative colitis have been associated with combined oral contraceptive use such as ELOINE PLUS.

Chloasma may 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 ELOINE PLUS.

The administration of folates such as contained in ELOINE PLUS may mask vitamin B_{12} deficiency.

Reduced efficacy:

The efficacy of ELOINE PLUS may be reduced in the event of e.g. missed hormone-containing pink film-coated tablets, gastro-intestinal disturbances (section "Advice in case of gastro-intestinal disturbances" – under "Dosage and Directions for Use") during hormone-containing pink film-coated tablet taking or concomitant medication (section "Effects of other medicines on ELOINE PLUS" and "Other forms of interactions" under "Interactions").

Reduced cycle control:

Irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use.

In some women withdrawal bleeding may not occur during the hormone-free light orange film-coated tablet phase. If ELOINE PLUS has been taken according to the "Dosage and directions for use", it is unlikely that the woman is pregnant. However, if ELOINE PLUS has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before ELOINE PLUS use is continued.

Medical examination/consultation:

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of ELOINE PLUS use, guided by the "Contra-indications" and "Warnings", and should be repeated periodically. Periodic medical assessment is also of importance because contra-indications (e.g. a transient ischaemic attack, etc) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a ELOINE PLUS. The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman, but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology.

Women should be advised that ELOINE PLUS does not protect against HIV infections (AIDS) and other sexually transmitted diseases (STDs). Women should be advised that additional barrier contraceptive measures are needed to prevent transmission of STDs and HIV.

Lactose intolerance:

Each pink tablet contains 45 mg lactose and each light orange tablet contains 48 mg. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

INTERACTIONS:

Effects of other medicines on ELOINE PLUS:

Interactions between ELOINE PLUS and other medicines (enzyme inducers, some antibiotics) may lead to breakthrough bleeding and/or contraceptive failure.

Women on treatment with any of these medicines should temporarily use a barrier method in addition to ELOINE PLUS 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. Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after discontinuation. If the period during which the barrier method is used runs beyond the end of the hormone-containing pink film-coated tablets in the ELOINE PLUS pack, the hormone-free light orange film-coated tablets should be omitted and the next ELOINE PLUS pack be started.

Substances diminishing the efficacy of ELOINE PLUS (enzyme-inducers and antibiotics):

Enzyme induction (increase of hepatic metabolism):
Interactions can occur with medicines that induce microsomal enzymes, which can result in increased clearance of sex hormones (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John's Wort).
Also, HIV protease inhibitors (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g.

nevirapine), and combinations of them, have been reported to potentially affect hepatic metabolism.

Antibiotics (Interference with enterohepatic circulation):
Some clinical reports suggest that enterohepatic circulation of estrogens may decrease when certain antibiotic agents are given, which may reduce ethinylestradiol concentrations (e.g. penicillins, tetracyclines).

Substances diminishing the efficacy of levomefolate calcium:

Folate metabolism:
Several medicines have been reported to reduce folate levels and decrease the efficacy of folates by inhibition of the human dihydrofolate reductase (e.g. methotrexate, trimethoprim, sulfasalazine, and triamterene) or by reducing folate absorption (e.g. cholestyramine), or via unknown mechanisms (e.g. antiepileptics medicines such as carbamazepine, phenytoin, phenobarbital and primidone and valproic acid).

Substances interfering with the metabolism of ELOINE PLUS (enzyme inhibitors):

The main metabolites of drospirenone in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of drospirenone.

Effects of ELOINE PLUS or levomefolate calcium on other medicines:

ELOINE PLUS may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

Based on *in vitro* inhibition studies and *in vivo* interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrates, an interaction of drospirenone at doses of 3 mg with the metabolism of other medicines is unlikely.

Folates may modify the pharmacokinetics or pharmacodynamics of certain antifolate medicines, e.g. antiepileptics (such as phenytoin), methotrexate or pyrimethamine and may result in a decreased pharmacological effect of the antifolate medicine.

Other forms of interactions:

Serum potassium:
There is a potential for an increase in serum potassium in women taking ELOINE PLUS hormone-containing pink film-coated tablets with other medicines that may increase serum potassium levels. Such medicines include angiotensin-II-receptor antagonists, potassium-sparing diuretics, and aldosterone antagonists. However, in studies evaluating the interaction of drospirenone (combined with estradiol) with an ACE inhibitor or indomethacin, no clinically or statistically significant differences in serum potassium concentrations were observed.

Laboratory tests:

The use of contraceptive steroids may influence the results of 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 carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range. Drospirenone causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

No formal interaction studies were carried out with tuberculosis or HIV treatments.

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

PREGNANCY AND LACTATION:

Pregnancy:

ELOINE PLUS is not indicated during pregnancy. If pregnancy occurs during treatment with ELOINE PLUS, further intake must be stopped. Women stopping ELOINE PLUS should consider continuation of folate supplementations.

Lactation:

The use of ELOINE PLUS is not recommended during breastfeeding. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk.

DOSAGE AND DIRECTIONS FOR USE:

Method of administration

Oral Use.

ELOINE PLUS, when taken correctly, has a failure rate of approximately 1 % per year. The failure rate may increase when pills are missed or taken incorrectly.

Tablets must be taken in the order directed on the package, at about the same time every day, with some liquid if needed. Tablet taking is continuous. One tablet is taken daily for 28 consecutive days.

The first course of ELOINE PLUS is started on the first day of the menstrual period (day 1 of the cycle) from the silver section of the pack by selecting the appropriate tablet for that day of the week (e.g. "MO" for Monday). The tablet is swallowed whole with some liquid. Thereafter one tablet must be taken daily for 28 days following the direction shown by the arrows. It does not matter at what time of the day the tablet is taken, but once the patient has selected a particular time, the tablet should be taken as near as possible at the same time each day.

Each subsequent pack is started the day after the last intake of the previous pack. A withdrawal bleed usually starts on day 2 to 3 after starting the hormone-free light orange film-coated tablets (last row) and may not have finished before the next pack is started.

How to start ELOINE PLUS:

No preceding hormonal contraceptive use (in the past month):
Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). For example, if her period starts on a Friday, start with the tablet marked "FR". Starting on days 2 to 5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

Changing from a combined hormonal contraceptive (combined oral contraceptive), vaginal ring, or transdermal patch:
The woman should start with ELOINE PLUS preferably on the day after the last hormone-containing tablet of her previous combined oral contraceptive, but at the latest on the day following the usual tablet-free or inactive tablet interval of her previous combined oral contraceptive. In case a vaginal ring or transdermal patch has been used, the woman should start using ELOINE PLUS preferably on the day of removal, but at the latest when the next application would have been due.

Changing from a progestogen-only method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS):
The woman may switch any day from the minipill, from an implant or the intrauterine system on the day of its removal and from an injectable when the next injection would be due, but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

Following first-trimester abortion:
The woman may start immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second-trimester abortion:
For breastfeeding women see "Pregnancy and lactation".
Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When

starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of ELOINE PLUS or the woman has to wait for her first menstrual period.

Management of missed tablets:

Missed hormone-free light orange film-coated tablets can be disregarded. However, they should be discarded to avoid unintentionally prolonging the hormone-free light orange tablet phase. The following advice only refers to **missed hormone-containing pink** film-coated tablets:

If the user is ***less than 12 hours*** late in taking any hormone-containing tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is ***more than 12 hours*** late in taking any hormone-containing tablet, contraceptive protection may be reduced. The management of missed hormone-containing tablets can be guided by the following two basic rules:

1. Active tablet-taking must never be discontinued for longer than 4 days;
2. 7 days of uninterrupted hormone-containing tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

Day 1 to 7:
The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets that are missed and the closer they are to the hormone-free tablet phase, the higher the risk of a pregnancy.

Day 8 to 14:
The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions (barrier method e.g. condom) for 7 days.

Day 15 to 24:
The risk of reduced reliability is imminent because of the forthcoming hormone-free light orange film-coated tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. If either of the following two options is adhered to, there is no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options, and to use extra precautions (barrier method e.g. condom) for the next 7 days as well.

1. The user should take the last missed hormone-containing pink film-coated tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until the hormone-containing pink tablets are used up. The 4 hormone-free light orange tablets must be discarded. The next pack must be started right away. The user is unlikely to have a withdrawal bleed until the end of the hormone-containing pink tablets section of the second pack, but she may experience spotting or breakthrough bleeding on active tablet-taking days.
2. The woman may also be advised to discontinue taking the pink film-coated tablets from the current pack. She should then have a tablet-free interval of up to 4 days, including the days she missed tablets, and subsequently continue with the next pack, starting with the hormone-containing pink tablet for the appropriate day of the week.

If the woman missed tablets and subsequently has no withdrawal bleed in the hormone-free light orange tablet phase, the possibility of a pregnancy should be considered.

Advice in case of gastrointestinal disturbances:

In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3 to 4 hours after taking the pink hormone-containing tablet, the advice concerning missed tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she must take the extra tablet(s) needed from another pack.

How to delay a period:

To delay a period the woman should continue with another pack of ELOINE PLUS without taking the hormone-free light orange film-coated tablets from her current pack. The extension can be carried on for as long as wished until the end of the pink film-coated tablets in the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of ELOINE PLUS is then resumed after the hormone-free light orange tablet phase of the second pack.

Additional information on special populations:

Children and adolescents:

ELOINE PLUS is only indicated after menarche.

Patients with hepatic impairment:

ELOINE PLUS is contra-indicated in women with severe hepatic diseases. See also sections “Contra-indications” and “Pharmacokinetic properties”.

Patients with renal impairment:

ELOINE PLUS is contra-indicated in women with severe renal insufficiency or acute renal failure. See also sections “Contra-indications” and “Pharmacokinetic properties”.

SIDE EFFECTS:

The frequencies of adverse reactions (ARs) reported in clinical trials (N= 2 614) with Yasmin (Reg. No:34/18.8/0494) are summarised in the table below. The Yasmin adverse reactions are also regarded as being representative for YASMIN PLUS/ELOINE PLUS (the only addition being the vitamin levomefolate calcium as a stable salt of the naturally occurring form of folates found in foods). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) and rare (≥ 1/10 000 to < 1/1 000).

System organ class (MedDRA v. 12.0)	Common	Uncommon	Rare
Metabolism and nutrition disorders		Body weight changes Fluid retention	
Psychiatric disorders	Depressive mood	Changes in libido	
Nervous system disorders	Headache Migraine		
Ear and labyrinth disorders			Hypacusia
Vascular disorders		Hypertension Hypotension	Thromboembolism
Respiratory, thoracic and mediastinal disorders			Asthma
Gastrointestinal disorders	Nausea	Vomiting	
Skin and subcutaneous tissue disorders		Acne Eczema Pruritus	
Reproductive system	Breast pain*	Vaginitis	Breast discharge

and breast disorders	Leukorrhoea** Vaginal moniliasis Menstrual disorder Intermenstrual bleeding***		

* including breast tenderness
** including vaginal discharge
*** bleeding irregularities usually subside during continued treatment

The following serious adverse events have been reported in women using combined oral contraceptives, which are discussed in the "Warnings" section:

- Venous thromboembolic disorders,
- Arterial thromboembolic disorders,
- Cerebrovascular accidents,
- Hypertension,
- Hyperkalaemia (in patients with renal impairment and pre-treatment upper reference range serum potassium levels),
- Hypertriglyceridaemia,
- Changes in glucose tolerance or effect on peripheral insulin resistance,
- Liver tumours (benign and malignant),
- Liver function disturbances,
- Chloasma,
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema,
- Occurrence or deterioration of: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss, Crohn's disease, ulcerative colitis, cervical cancer.

The frequency of diagnosis of breast cancer is slightly increased among oral contraceptives users. Causation with combined oral contraceptives use is unknown. For further information, see sections "Contra-indications" and "Warnings".

The following adverse reactions have been identified worldwide during postapproval use of ELOINE PLUS:

- Immune system disorder: hypersensitivity,
- Psychiatric disorder: altered mood,
- Eye disorder: contact lens intolerance,
- Gastrointestinal disorders: abdominal pain, diarrhoea,
- Skin and subcutaneous tissue disorders: rash, urticarial, erythema nodosum, erythema multiforme,
- Reproductive system and breast disorders: breast enlargement.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

On the basis of general experience with combined oral contraceptives, symptoms that may occur in case of taking an overdose of hormone-containing tablets are: nausea; vomiting; and, in young girls, slight vaginal bleeding. Treatment should be symptomatic and supportive.

IDENTIFICATION:

24 pink, round, biconvex active film-coated tablets, with one side embossed with "Z+" in a regular hexagon, while the other side is blank PLUS 4 light orange, round, biconvex hormone-free film-coated tablets, with one side embossed with "M+" in a regular hexagon, while the other side is blank.

PRESENTATION:

ELOINE PLUS is packed in colourless transparent high barrier PVC/PE.EVOH.PE/PCTFE/ aluminium blisters containing 24 pink film-coated hormonal tablets plus 4 light orange hormone-free film-coated tablets per blister strip packed in a hermetic pouch (PET/Al/PE). The pouch is packed into an outer cardboard carton.
Pack sizes: 28 tablets: 1 x (24 + 4) tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.
Keep the blister strip in the pouch, in the original carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

55/21.8.2/0463

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
ISANDO,1609

DATE OF PUBLICATION OF THE PACKAGE INSERT

Registration date: 19 April 2022
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