SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

ELOINE®
Film-coated tablets

COMPOSITION:

The 28-day pack (Every-Day pack) contains 24 hormonal tablets each with 3 mg drospirenone and 0,02 mg ethinylestradiol as betadex clathrate, plus 4 inactive tablets.
Contains lactose monohydrate.

Excipients:
Ferric oxide red (E172), hypromellose 5 cP, lactose monohydrate, magnesium stearate, maize starch, povidone K25, talc, titanium dioxide (E171).

PHARMACOLOGICAL CLASSIFICATION:

A 21.8.2 Progesterones with oestrogens

PHARMACOLOGICAL ACTION:

Pharmacological 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, oestrogenic, glucocorticoid and antiglucocorticoid activity.

Pharmacokinetic properties:

- **Drospirenone**

Absorption:

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations of the active substance in serum of about 35 ng/ml are reached at about 1 to 2 hours after single ingestion. Bioavailability is between 76 and 85 %. The intake of food had no influence on the extent of absorption of drospirenone, 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 active substance 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 did not show any clinically significant effect on serum potassium concentration.

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 Cmax values. The decline in serum drospirenone concentrations during the terminal disposition phase was about 1,8 times greater for the volunteers with moderate hepatic impairment 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.

INDICATIONS:

- Oral contraceptive.
- 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 for PMDD was not assessed beyond 3 cycles.

ELOINE has not been evaluated for treatment of premenstrual syndrome (PMS).

CONTRA-INDICATIONS:

Combined oral contraceptives such as ELOINE 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, the product should be stopped immediately.

- 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).
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis (see “Warnings”).
- 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.
- Hypersensitivity to the active substances or to any of the excipients.

WARNINGS:

Circulatory disorders:

Epidemiological studies have suggested an association between the use of ELOINE and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism.

The risk of VTE is highest during the first year of use. This increased risk is present after initially starting ELOINE 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 oestrogen 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 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/m²);
- 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 use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the ELOINE.

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 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. The excess risk gradually disappears during the course of the 10 years after cessation of ELOINE use.

Benign liver tumours and, even more rarely, malignant liver tumours have been reported in users of ELOINE. In isolated cases, 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.

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.

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

The occurrence or deterioration of the following conditions have been reported with ELOINE 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 oestrogens such as ELOINE may induce or exacerbate symptoms of angioedema.

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

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

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

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.

Medical examination/consultation:

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of ELOINE 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 ELOINE. 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 and relevant laboratory tests.

Women should be advised that ELOINE 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 infection.

Reduced efficacy:

The efficacy of ELOINE may be reduced in the event of e.g. missed active tablets, gastro-intestinal disturbances during active tablet taking (see "Dosage and directions for use") or concomitant medication (see "Interactions").

Reduced cycle control:

Irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the inactive tablet phase. If ELOINE has been taken according to the directions described under "Dosage and directions for use", it is unlikely that the woman is pregnant. However, if ELOINE 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 use is continued.

INTERACTIONS:

Interactions between ELOINE and other medicines may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

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 (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and combinations of them, have been reported to potentially affect hepatic metabolism.

Interference with enterohepatic circulation:

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

Women on treatment with any of these medicines should temporarily use a barrier method in addition to ELOINE 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 active tablets in the ELOINE pack, the inactive tablets should be omitted and the next pack of ELOINE should be started with the active tablets in the white section (i.e. without the usual inactive tablet interval).

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.

ELOINE may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations either increase (e.g. cyclosporin) 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.

Other interactions:

There is a potential for an increase in serum potassium in women taking ELOINE 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.

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.

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.

PREGNANCY AND LACTATION:

ELOINE is not indicated during pregnancy. If pregnancy occurs during treatment with ELOINE, further intake should be stopped.

The use of ELOINE 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, 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. One tablet is taken daily for 28 days. 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 placebo tablets (white tablets in the last row) and may not be finished before the next pack is started.

How to start ELOINE:

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). 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 preferably on the day after the last active 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 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:

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 use or the woman has to wait for her first menstrual period.

Management of missed tablets:

Missed white pills (from the last row of the blister) are placebo and thus can be disregarded to avoid unintentionally prolonging the placebo tablet phase. The following advice only pertains to missed active tablets:

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

1. Active tablet-taking must never be discontinued for longer than four days;
2. 7 days of uninterrupted active 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 inactive 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 for 7 days.

Day 15 to 24:

The risk of reduced reliability is imminent because of the forthcoming inactive 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 use extra precautions for the next 7 days as well.

1. 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 until the active tablets are used up. The 4 inactive 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 active 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 active tablet-taking 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 in the white section with the tablet for the appropriate day of the week.
   If the woman missed active tablets and subsequently has no withdrawal bleed in the inactive 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 active tablet-taking, 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 without taking the inactive tablets from her current pack. The extension can be carried on for as long as wished until the end of the active tablets in the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of ELOINE is then resumed after the inactive tablet phase.

Additional information on special populations:

Children and adolescents:

ELOINE is only indicated after menarche.

Elderly patients:

ELOINE is not indicated after menopause.

Patients with hepatic impairment:

ELOINE is contra-indicated in women with severe hepatic diseases as long as liver function values have not returned to normal. See also section "Contra-indications".

Patients with renal impairment:

ELOINE is contra-indicated in patients with severe renal impairment or acute renal failure. (see "Contra-indications").

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

The frequencies of adverse reactions (ARs) reported in clinical trials with drospirenone/ethinylestradiol are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), 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 and breast disorders	Breast pain* Leukorrhoea** Vaginal moniliasis Menstrual disorder Intermenstrual bleeding***	Vaginitis	Breast discharge

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

The most appropriate MedDRA term to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

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 oestrogens as contained in ELOINE 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 post approval use of ELOINE:

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.

Special precautions:

Medical examination/consultation:

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of ELOINE 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 ELOINE. 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 and relevant laboratory tests.

Women should be advised that ELOINE 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 infection.

Reduced efficacy:

The efficacy of ELOINE may be reduced in the event of e.g. missed active tablets, gastro-intestinal disturbances during active tablet taking (see “Dosage and directions for use”) or concomitant medication (see “Interactions”).

Reduced cycle control:

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

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the inactive tablet phase. If ELOINE has been taken according to the directions described under “Dosage and directions for use”, it is unlikely that the woman is pregnant. However, if ELOINE 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 use is continued.

Effects on ability to drive or use machines:

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of combined oral contraceptives such as ELOINE.

Lactose intolerance:

Each light pink tablet contains 48 mg lactose and each white tablet contains 52 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.

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 active tablets are: nausea; vomiting; and, in young girls, slight vaginal bleeding. Treatment should be symptomatic and supportive.

IDENTIFICATION:

24 light, pink, active, round film-coated tablets with convex faces, one side embossed with the letters “DS” in a regular hexagon. 4 white, inactive, round film-coated tablets with convex faces, one side embossed with the letters “DP” in a regular hexagon.

PRESENTATION:

Cartons containing one blister strip with 28 tablets. Blister packs consist of transparent films made of polyvinyl chloride and metallic foils made of aluminium (mat side hot sealable).

STORAGE INSTRUCTIONS:

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

REGISTRATION NUMBER:

44/21.8.2/0957

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:

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