SCHEDULING STATUS S3

PROPRIETARY NAME AND DOSAGE FORM

FEMODENE ED

Tablets

COMPOSITION

The 28-day pack (Every-Day pack) contains 21 hormonal tablets each with gestodene (17α-ethinyl-13-ethyl-17β-hydroxy-4,15-gonadiene-3-one) 0,075 mg and ethinylestradiol (17α-ethinyl-estra-1,3,5(10)-triene-3,17β-diol) 0,03 mg, plus 7 inactive tablets.

PHARMACOLOGICAL CLASSIFICATION

A. 21.8.2 Progesterones with estrogens.

PHARMACOLOGICAL ACTION

Pharmacodynamics

Femodene ED is a low-dose monophasic oral contraceptive with estrogenic and progestogenic peripheral effects.

The contraceptive effect of Femodene ED 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.

Pharmacokinetics

- Gestodene

Absorption
Orally administered gestodene is rapidly and completely absorbed. Peak serum concentrations of 4 ng/ml are reached at about 1 hour after single ingestion. Bioavailability is about 99%.

Distribution
Gestodene is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1 to 2 % of the total serum drug concentration is present as free steroid, 50 to 70% is specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the distribution over the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of gestodene is 0,7 l/kg.

Metabolism
Gestodene is completely metabolised by the known pathways of steroid metabolism. The metabolic clearance rate from the serum is 0,8 ml/min/kg. No interaction was found with the coadministered ethinylestradiol.

Elimination
Gestodene serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of 12 to 15 hours. Gestodene is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 6:4. The half-life of metabolite excretion is about 1 day.

Steady-state conditions
Gestodene pharmacokinetics are influenced by SHBG levels, which are increased threefold by ethinylestradiol. Following daily ingestion, drug serum levels increase about fourfold reaching steady-state conditions during the second half of a treatment cycle.

- Ethinylestradiol

Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 80 pg/ml are reached within 1 to 2 hours. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60%.

Distribution
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 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 is about 5 ml/min/kg.

Elimination
Ethinylestradiol serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 24 hours. Unchanged drug is not excreted, ethinylestradiol metabolites 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 after 3 to 4 days when serum drug levels are higher by 30 to 40% as compared to single dose.

INDICATIONS

Oral contraception.

CONTRA-INDICATIONS

Combined oral contraceptives 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 combined oral contraceptive use, the product should be stopped immediately.

- Thrombosis (venous or arterial) present or in history (eg deep venous thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident).
- Presence or history of prodromi of a thrombosis (eg transient ischaemic attack, angina pectoris).
- Diabetes mellitus with vascular involvement.
- The presence of a multiple risk factor(s) for venous or arterial thrombosis (such as eg hypertension, a family history of thromboembolic events, prolonged immobilisation – see further risk factors for thromboembolism under “Warnings - Circulatory disorders” below) may also constitute a contra-indication.
- Presence or history of hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected malignant conditions of the genital organs or the breasts, if sex steroid-influenced.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to any of the components of Femodene ED.

WARNINGS

If any of the conditions/risk factors mentioned below are present, the benefits of combined oral contraceptive use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether its use should be discontinued.

Circulatory disorders

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

Venous thromboembolism, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all combined oral contraceptives.

Thrombosis has been reported to occur in other blood vessels, eg hepatic, mesenteric, renal or retinal veins and arteries, in combined oral contraceptive users.

Symptoms of venous or arterial thrombosis can include: unilateral leg pain and/or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen.

The risk of thromboembolism (venous and/or arterial) increases with:

- age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- a positive family history (ie 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;
- 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.

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

The onset of, or increase in frequency or severity of migraine during combined oral contraceptive use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the combined oral contraceptive.

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).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with combined oral contraceptive use.

Tumours

An increased risk of cervical cancer in long-term users of combined oral contraceptives has been reported in epidemiological studies.

A meta-analysis from epidemiological studies reported that there is an increased relative risk of having breast cancer diagnosed in women who are currently using combined oral contraceptives.

Benign liver tumours, and rarely, malignant liver tumours have been reported in users of combined oral contraceptives. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. 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 combined oral contraceptives.

Other conditions

- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using combined oral contraceptives.
- Small increases in blood pressure have been reported in many women taking combined oral contraceptives; clinically relevant increases may occur. If a sustained clinically significant hypertension develops during the use of a combined oral contraceptive then it is prudent for the physician to withdraw the combined oral contraceptive and treat the hypertension. Where considered appropriate, combined oral contraceptive use may be resumed if normotensive values can be achieved with antihypertensive therapy.
- The following conditions have been reported to occur or deteriorate with combined oral contraceptive 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.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of combined oral contraceptive use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of combined oral contraceptives.
- Although combined oral contraceptives may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using combined oral contraceptives. However, diabetic women should be carefully observed while taking combined oral contraceptives.
- Crohn's disease and ulcerative colitis have been associated with combined oral contraceptive use.
- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking combined oral contraceptives.
- Respiratory: Asthma may deteriorate in women using combined oral contraceptives.

DOSAGE AND DIRECTIONS FOR USE

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of combined oral contraceptive use, guided by the "Contra-indications" and "Warnings" and should be repeated at least annually during the use of combined oral contraceptives. Periodic medical assessment is also of importance because contra-indications (eg a transient ischaemic attack, etc) or risk factors (eg a family history of venous or arterial thrombosis) may appear for the first time during the use of a combined oral contraceptive. The frequency and nature of these assessments should 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.

How to take Femodene ED

The first course of Femodene ED 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 (eg "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. Withdrawal bleeding usually starts on day 2 to 3 after starting the inactive tablets and may not have finished before the next pack is started. Each subsequent pack is started the day after the last tablet of the current pack. If a patient starts Femodene ED during the latter part of the week, the very first cycle may be slightly shortened.

How to start Femodene ED

No preceding hormonal contraceptive use (in the past month)
Tablet-taking has to start on day 1 of the woman's natural cycle (ie the first day of her menstrual bleeding). If the woman starts with an inactive tablet on day 1, she should be advised to additionally use a barrier method for the first 14 days of tablet-taking.

Changing from another combined oral contraceptive
The woman should start with Femodene ED preferably on the day after the last active tablet of her previous combined oral contraceptive.

Changing from a progestogen-only-method (minipill, injection, implant)
The woman may switch any day from the minipill (from an implant on the day of its removal, 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 14 days of tablet-taking.

Following first trimester abortion
The woman may start immediately. She should be advised to additionally use a barrier method for the first 14 days of tablet-taking.

Following delivery or second-trimester abortion
For breastfeeding women see "Side-effects and special precautions". Women should be advised to start at day 21 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 14 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of combined oral contraceptive use or the woman has to wait for her first menstrual period.

Management of missed tablets

The large white tablets are inactive tablets and missing these can be disregarded. However, they should be discarded to avoid unintentionally prolonging the inactive tablet phase. The following advice only refers 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 tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

- Tablet-taking must never be discontinued for longer than 7 days.
- 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:

If you are ***less than 12 hours*** late in taking your Femodene ED tablet, you are still protected against pregnancy. Take the tablet as soon as you remember and take the next one at your usual time. This may mean that you are taking 2 tablets in one day.

If you are ***more than 12 hours*** late in taking your Femodene ED tablet you will not be protected. Take the tablet as soon as you remember and take the next one at your normal time. This may mean taking 2

tablets in one day. You must take extra contraceptive precautions and you must follow the 7 day rule. Read the sections on “Extra contraceptive precautions” and “The 7 day rule” carefully.

If you have forgotten to take your Femodene ED tablets for a few days, consult your doctor to be sure you are not pregnant, then discard the missed tablets and follow the 7 day rule.

Extra contraceptive precautions
When you need extra contraceptive precautions, either:
- don’t have sex; or
- use a cap plus spermicide, or a condom.

Don’t use the rhythm or temperature methods as extra contraceptive precautions. This is because oral contraceptives disrupt the usual menstrual cycle changes such as changes in temperature and cervical mucus.

The 7 day rule
If:
- you are more than 12 hours late in taking a tablet; or
- you have vomiting; or
- your doctor advises you to follow the 7 day rule because you are taking certain medicines;

continue to take your tablets as usual.
However, take extra contraceptive precautions during the next 7 days, BUT - if these days run beyond the end of the small white active tablets in your pack - the 7 large white inactive tablets must NOT be taken (ie discard the current pack after taking the last small tablet on “FR”). Start a new pack the next day with the “SA” tablet from the silver section. You can now continue pill taking as before. Read the section “Extra contraceptive precautions” carefully.
Do not leave a gap between packs. Your menstrual period will occur after you have completed the second pack. If the period does not occur, consult your doctor before resuming the next pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the inactive tablet phase, the possibility of a pregnancy should be considered.

Advice in case of vomiting

If vomiting occurs within 3 to 4 hours after active tablet-taking, absorption may not be complete. In such an event, the advice under the section “Management of missed tablets” is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to 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 Femodene ED 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 Femodene ED is then resumed after the inactive tablet phase.

Reduced cycle control

With all combined oral contraceptives, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

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

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects

Serious adverse effects

See “Warnings”.

Other possible adverse effects

The following adverse effects have been reported in users of combined oral contraceptives: breast tenderness, pain, secretion; headache; migraine; changes in libido; depressive moods; contact lens intolerance; nausea; vomiting; changes in vaginal secretion; various skin disorders including pigmentation; fluid retention; change in body weight; hypersensitivity reaction.

Special precautions

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmissible diseases.

Reduced efficacy: The efficacy of combined oral contraceptives may be reduced in the event of missed tablets, vomiting or concomitant medication.

Interactions

Drug interactions which result in an increased clearance of sex hormones can lead to breakthrough bleeding and oral contraceptive failure. This has been established with hydantoins, barbiturates, primidone, carbamazepine and rifampicin; oxcarbazepine, topiramate, felbamate and griseolfulvin are also suspected. The mechanism of this interaction appears to be based on the hepatic enzyme-inducing properties of these drugs. Maximal enzyme induction is generally not seen for 2 to 3 weeks but may then be sustained for at least 4 weeks after the cessation of drug therapy.

Contraceptive failures have also been reported with antibiotics, such as ampicillins and tetracyclines. The mechanism of this effect has not been elucidated.

Women on short-term treatment with any of the abovementioned classes of drugs or individual drugs should temporarily use a barrier method in addition to the combined oral contraceptive, ie during the time of concomitant drug administration and for 7 days after their discontinuation. For women on rifampicin a barrier method should be used in addition to the combined oral contraceptive during the time of rifampicin administration and for 28 days after its discontinuation. If concomitant drug administration runs beyond the end of the active tablets in the current combined oral contraceptive pack, the inactive tablets must be discarded and the next combined oral contraceptive pack started right away.

In women on long-term treatment with hepatic enzyme-inducing drugs, the contraceptive steroid doses should be increased. If a high contraceptive dosage is not desirable or appears to be unsatisfactory or unreliable, eg in the case of irregular bleeding, another method of contraception should be advised. Oral contraceptives may interfere with the metabolism of other medicines. Accordingly plasma and tissue concentrations may be affected (eg benzodiazepines).

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, eg 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.

Pregnancy and lactation

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born

to women who used combined oral contraceptives prior to pregnancy, nor a teratogenic effect when combined oral contraceptives were taken inadvertently during early pregnancy. See also “Contra-indications”. Feminisation of the male foetus may occur.

Lactation may be influenced by combined oral contraceptives as they may reduce the quantity and change the composition of breast milk, therefore, the use of combined oral contraceptives should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk, but there is no evidence that this adversely affects infant health.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in case of taking an overdose of active tablets are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

IDENTIFICATION

21 small white coated hormonal tablets and 7 large white coated inactive tablets.

PRESENTATION

Carton with 1 calendar pack containing 28 tablets enclosed within a foil pouch.

STORAGE INSTRUCTIONS

Store at or below 30 °C. Protect from light. KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

W/21.8.2/98

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

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