**FEMME-TAB 20/100**
Levonorgestrel/Ethinyloestadiol Film-coated Tablets

**Name of the medicine**

Femme-Tab 20/100 is a combined oral contraception (COC) with 21 tablets containing the synthetic progestogen, levonorgestrel, and the synthetic oestrogen ethinyloestradiol.

**Physical and chemical characteristics**

The chemical name for Levonorgestrel is 13β-ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one and has the following structural formula:

![Structural formula of Levonorgestrel](image)

CAS number: 797-63-7  
Formula: C_{21}H_{28}O_2  
Molecular weight: 312.5

The chemical name for ethinyloestradiol is 19-nor-17α-pregna-1,3,5(10)-tri-en-20-yn-3,17-diol and has the following structural formula:

![Structural formula of Ethinyloestradiol](image)

CAS number: 57-63-6  
Formula: C_{20}H_{24}O_2  
Molecular weight: 296.4

**Description**

Levonorgestrel is a white or almost white, odourless or almost odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol, in acetone, and in ether; soluble in chloroform; sparingly soluble in methylene chloride.

Ethinyloestadiol is a white to creamy white, odourless, crystalline powder. It is practically insoluble in water and soluble in alcohol, chloroform, ether, vegetable oils, and aqueous solutions of alkali hydroxides.

Each white to off white tablet contains ethinyloestradiol 20 µg and levonorgestrel 100 µg and the excipients: lactose monohydrate, maize starch, gelatine, magnesium stearate, hypromellose (3cps), macrogol 4000, and titanium dioxide (E171).
Pharmacology

The hormonal components of Femme-Tab 20/100 inhibit ovulation by suppressing gonadotrophin release. Secondary mechanisms which may contribute to the effectiveness of Femme-Tab 20/100 as a contraceptive include changes in the cervical mucus (which increase the difficulty of sperm penetration) and changes in the endometrium (which reduce the likelihood of implantation).

Pharmacokinetics

The pharmacokinetic information provided is derived from a pharmacokinetic study using a single tablet containing ethinyloestradiol 20 µg and levonorgestrel 100 µg conducted in 20 women.

Levonorgestrel

Absorption

Levonorgestrel is absorbed quickly and completely. Maximum active substance levels of approx. 2.4 ng/mL were reached in serum approximately 1.0-1.3 hours after ingestion of one tablet containing ethinyloestradiol 20 µg and levonorgestrel 100 µg. The serum concentrations subsequently fall in at least 2 disposition phases with a terminal half-life of around 24 hours. The metabolic clearance rate, including the bound component, from plasma is approx 1.0 mL/min/kg.

Distribution

Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only around 1.1% of the total serum medicine concentrations are present as free steroid, approximately 65% are specifically bound to SHBG. The relative proportions (free, albumin-bound, SHBG-bound) depend on the concentration of SHBG. After induction of the binding protein, the portion bound to SHBG increases to 75%, while the free portion and that bound to albumin decrease to around 0.8 and 25%, respectively.

After daily repeated ingestion, levonorgestrel accumulates by about the factor of 3. A steady state is reached after approximately 11 days. The pharmacokinetics of levonorgestrel are nonlinear due to an increase in binding of levonorgestrel to SHBG which is attributed to increased SHBG levels that are induced by the daily administration of ethinyloestradiol. The levonorgestrel serum levels do not change any further after 1-3 cycles of use because SHBG induction is concluded. The absolute bioavailability of levonorgestrel amounts to almost 100%.

Metabolism

Extensive reduction of the α, β-unsaturated ketone in ring A occurs, in addition to hydroxylation at carbons 2 and 16 to form dihydro and tetrahydro reduced products. Metabolites may circulate as sulfates or glucuronides, however most of the metabolites that circulate in the blood are sulfates of 3α, 5β-tetrahydro-levonorgestrel. There are also large amounts of unconjugated levonorgestrel in the circulation with small amounts of unconjugated and/or conjugated forms of 3α, 5β-tetrahydrolevonorgestrel and 16β-hydroxylevonorgestrel. Excretion occurs predominantly in the form of glucuronides.
Elimination
Levonorgestrel is eliminated in the form of metabolites with a half-life of approximately $28 \pm 7$ hours and in almost equal proportions via the kidney and bile.

Ethinyloestriadiol

Absorption
Orally administered ethinyloestriadiol is absorbed quickly and almost completely from the gastrointestinal tract but due to first-pass metabolism in gut mucosa and liver, the absolute bioavailability of ethinyloestriadiol is subject to considerable interindividual variations. After oral ingestion, it amounts to around 40-60% of the dose.

Ingestion of tablets containing ethinyloestriadiol 20 µg and levonorgestrel 100 µg leads to maximum plasma levels of approx. 50 pg/mL after 1-2 hours. The substance concentration then falls in at least 2 disposition phases with a terminal half-life of around 24 hours. For technical reasons, these data can only be calculated at higher dosages.

Distribution
Ethinyloestriadiol is bound non-specifically to serum albumin to about 98%. Ethinyloestriadiol does not bind to SHBG but induces SHBG synthesis.

Metabolism
Cytochrome P450 enzymes (CYP3A4) in the liver are responsible for the 2-hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and faecal excretion. Levels of Cytochrome P450 (CYP3A4) vary widely amongst individuals and may explain the variations in rates of ethinyloestriadiol 2-hydroxylation. Ethinyloestriadiol is excreted in the urine and faeces as glucuronide and sulphate conjugates, and undergoes enterohepatic circulation.

Elimination
Ethinyloestriadiol is eliminated in the form of metabolites with a half-life of around 18±4.7 hours at steady state. The excretion ratio is 40 (urine): 60 (bile).

Clinical Trials
An open-label, non-comparative multi-centre phase III clinical study was conducted in 820 women receiving COC tablets containing ethinyloestriadiol 20 µg and levonorgestrel 100 µg for a planned individual maximum of 6 cycles. (Study 1) Six cycles were completed by 680 women. 4,400 cycles in which no alternative methods of contraception were used were available for the efficacy analysis. One pregnancy was reported. This represents an overall user-efficacy (typical user-efficacy) pregnancy rate of 0.32 per 100 women years (over 99% effective at preventing pregnancy). This rate includes patients who missed up to 3 tablets per cycle. The overall compliance (no missed tablets) was between 94.6% and 98.4% over the course of the study.

Published data from a larger study with a similar preparation containing the same dosage of active ingredients in 1447 women, with 7720 cycles of exposure, reports 5 pregnancies and an overall user-efficacy pregnancy rate of 0.84 per 100 women years, in women who missed up to 3 tablets consecutively per cycle or 5 non-consecutive tablets per cycle.
The overall user-efficacy pregnancy rates for COC tablets containing ethinyloestradiol 20 µg and levonorgestrel 100 µg and other forms of contraception from a number of non-comparative trials based on historical data are given below:

<table>
<thead>
<tr>
<th>Oral contraceptive</th>
<th>Overall user-efficacy (Pearl Index)</th>
<th>Effectiveness* at preventing pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 µg levonorgestrel 20 µg ethinyloestradiol</td>
<td>0.32</td>
<td>99.68%</td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 µg levonorgestrel 20 µg ethinyloestradiol</td>
<td>0.84</td>
<td>99.16%</td>
</tr>
<tr>
<td>150 µg levonorgestrel 30 µg ethinyloestradiol</td>
<td>0.30-0.35</td>
<td>99.65% - 99.7%</td>
</tr>
<tr>
<td>30 µg levonorgestrel</td>
<td>0.30-3.0</td>
<td>97.00% - 99.7%</td>
</tr>
</tbody>
</table>

* 100%-(Pearl Index) = User effectiveness per 100 women years. (e.g if 100 women took oral contraceptive tablets for 1 year the chance of an accidental pregnancy would be less than 1%).

The contraceptive efficacy of the levonorgestrel 100 µg/ethinyloestradiol 20 µg formulations ranges from 99.16-99.68%. Compared historically with the contraceptive efficacy of 99.7% for 150 µg levonorgestrel/30 µg ethinyloestradiol tablets, this represents a similar up to 2-fold increase in the risk of pregnancy.

Cycle control was also evaluated by analysing cycle characteristics such as duration and intensity of withdrawal bleeding and the incidence of breakthrough bleeding and amenorrhoea. A total of 4400 cycles were valid for cycle control analysis; the overall incidence of inter-menstrual bleeding was low. Although there was no comparative study of the cycle control of the lower dose COCs, compared with higher dosage COCs, cycle control data from historical studies with oral contraceptives containing higher doses of ethinyloestradiol and levonorgestrel are given in the table below:

<table>
<thead>
<tr>
<th>Dose*</th>
<th>Number of women</th>
<th>Number of cycles</th>
<th>Breakthrough bleeding (% cycles)</th>
<th>Spotting (% cycles)</th>
<th>Amenorrhoea (% cycles)</th>
<th>Cycle length (days)</th>
<th>Mean length of menstruation (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100/20</td>
<td>820</td>
<td>4400</td>
<td>4.5</td>
<td>12.4</td>
<td>4.5</td>
<td>26-30</td>
<td>4.7</td>
</tr>
<tr>
<td>150/30</td>
<td>1130</td>
<td>11064</td>
<td>6.0</td>
<td>7.7</td>
<td>1.8</td>
<td>26-30</td>
<td>4.3</td>
</tr>
<tr>
<td>150/30</td>
<td>325</td>
<td>3445</td>
<td>0.7</td>
<td>2.7</td>
<td>0.6</td>
<td>27-29</td>
<td>-</td>
</tr>
</tbody>
</table>

* Dose of levonorgestrel (µg)/ethinyloestradiol (µg). Note that the definitions of bleeding in these studies are not necessarily the same.

The length of withdrawal bleeding was 3-5 days for most patients (70%) (mean 4.7 days) and the intensity was scanty or normal for most subjects. Cycle length was between 26 and 30 days for most patients (up to 80%) with a tendency to be slightly shorter during the early cycles.

**Indications**

Femme-Tab 20/100 is used for oral contraception
Contraindications

Femme-Tab 20/100 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 their use, the product should be stopped immediately.

- Presence or 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 prodromi of a thrombosis (e.g. transient ischemic attack, angina pectoris)
- Diabetes mellitus with vascular involvement
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see also "Precautions ").
- Pancreatitis or a history thereof if associated with severe hypertriglyceridermia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant)
- History of migraine with focal neurological symptoms
- Known or suspected malignant conditions of the genital organs the breasts, or other organs, if sex steroid-influenced
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Hypersensitivity to any of the ingredients in Femme-Tab 20/100

Precautions

Use with caution in the following circumstances

If any of the conditions/risk factors mentioned below are present, the benefits of Femme-Tab 20/100 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 doctor. The doctor should then decide on whether Femme-Tab 20/100 use should be discontinued.

Circulatory Disorders

Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents. These events occur rarely.

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs. The risk for venous thromboembolism is highest during the first year a woman uses a COC. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months..

A large prospective 3-armed cohort study has shown that the frequency of VTE diagnosis range from 8 to 10 per 10,000 woman years in low oestrogen dose (< 50 µg ethinyloestradiol) COC users. The most recent data suggests that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman years in non-pregnant non-COC users.
and range from 20 to 30 per 10,000 pregnant women or post partum. Overall the risk of VTE in users of low oestrogen dose (< 50 µg ethinyloestradiol) COCs is two to threefold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

VTE may be fatal (in 1-2% of the cases).

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

Symptoms of venous (includes pulmonary embolism (PE) and deep venous thrombosis (DVT)) or arterial thrombotic/thromboembolic (includes myocardial infarction (MI), vascular occlusion and cerebrovascular accident) events can include: unilateral leg pain and/or swelling; pain or tenderness in the leg which may be felt only when standing or walking; increased warmth in the affected leg; red or discoloured skin on the leg; sudden severe pain in the chest which may increase with deep breathing; pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; rapid or irregular heartbeat; sudden onset of unexplained shortness of breath or rapid breathing; sudden onset of coughing which may bring up blood; sudden, severe prolonged headache with no known cause; sudden, partial or complete loss of vision; diplopia; sense of anxiety; dizziness; slurred speech or aphasia; sudden confusion; 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; fullness, indigestion or choking feeling; sweating; nausea; vomiting.

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

Arterial thromboembolic events may be fatal.

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 further increases, 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 known or suspected, the woman should be referred to a specialist for advice before deciding about any COC use.
- obesity (body mass index over 30 kg/m²)
- overweight
- dyslipoproteinemia
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation
- prolonged immobilisation (e.g. long haul flights), major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.
The increased risk of thromboembolism in the puerperium must be considered. (See also the "Use in Pregnancy" section).

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

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

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, 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 low-dose COCs (< 0.05 mg ethinyloestradiol).

**Tumours**

The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g. cervical screening and sexual behaviour including use of barrier contraceptives.

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 COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

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

**Other Conditions**

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC, then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.
The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver or kidney function may necessitate the discontinuation of COC use until markers of liver or kidney function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs 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 low-dose COCs (containing < 50 µg ethinyloestradiol). However, diabetic women should be carefully observed while taking COCs.

Crohn's disease and ulcerative colitis have been associated with COC 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 COCs.

Each white to off white tablet contains 36.56mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose:galactose malabsorption who are on a lactose free diet should take this amount into consideration.

Medical Examination/Consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of Femme:Tab 20/100 use, guided by the "Contraindications" and "Precautions" sections. This should be repeated periodically during the use of Femme:Tab 20/100. In general, an annual examination is recommended. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischemic 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 COC. 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.

Sexually transmitted diseases including HIV infections and AIDS

Femme-Tab 20/100 is intended to prevent pregnancy. It does not protect against sexually transmitted diseases (STDs), including HIV infections (AIDS). The woman should be advised that additional barrier contraceptive measures are needed to prevent transmission of STDs.

Reduced Efficacy

The efficacy of Femme-Tab 20/100 may be reduced in the event of missed white to off-white tablets, vomiting or diarrhoea during tablet taking or concomitant medication (see "Dosage and Administration").

Reduced Cycle Control
With all COCs, 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 tablet-free interval. If Femme-Tab 20/100 has been taken according to the directions described in the "Dosage and Administration" section, it is unlikely that the woman is pregnant. However, if Femme-Tab 20/100 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 Femme-Tab use is continued.

**Carcinogenicity**

Long-term continuous administration of natural and synthetic oestrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver. A long-term study with levonorgestrel in dogs showed an increased incidence of mammary tumours, although a similar effect was not apparent in studies in mice, rats or monkeys. The occurrence of these mammary tumours in dogs may be due in part to a hormonal feedback mechanism. The clinical relevance of these findings is uncertain.

Numerous epidemiological studies have been conducted to determine the incidence of breast, endometrial, ovarian and cervical cancer in women taking combination oral contraceptives. Some of these studies have shown an increased relative risk of breast cancer in certain subgroups of combination oral contraceptive users. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage. Some epidemiological studies also suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women, although there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV). It must also be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumours (also see Precautions).

**Genotoxicity**

There is limited evidence available in the literature suggesting that oestrogens may be weakly genotoxic at high doses. Ethinylestradiol was negative in studies for DNA-adduct formation in cultured human liver slices and in assays for gene mutations (bacterial or mammalian cells in vitro) and gave equivocal results in assays for chromosomal damage (clastogenic effects were not consistently seen and occurred at high doses).

The genotoxic potential of levonorgestrel has not been fully investigated, although limited data available to date suggest that it did not appear to be genotoxic.

**Use in Pregnancy (Category B3)**
The administration of Femme-Tab 20/100 is contraindicated during pregnancy. If pregnancy occurs during treatment with Femme-Tab 20/100, further intake should be stopped immediately.

Pregnancy Category B3. (Accumulated evidence reports that inadvertent exposure to these agents in early pregnancy has not been associated with an increased risk of birth defects).

Epidemiological studies have found no significant effects on foetal development in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy. See also "Contraindications".

Use in Lactation

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk. Therefore the use of Femme-Tab 20/100 should generally not be recommended until the nursing mother has completely weaned her child.

Use in children

Femme-Tab 20/100 is only indicated after menarche.

Use in the elderly

Femme-Tab 20/100 is not indicated after menopause.

Patients with hepatic impairment

Femme-Tab 20/100 is contraindicated in women with severe hepatic disease as long as liver function values have not returned to normal (see “Contraindications”)

Patients with renal impairment

Femme-Tab 20/100 has not been specifically studied in renally impaired patients

Interactions with Other Medicines

Interactions between oral contraceptives and other medicines may lead to breakthrough bleeding and/or oral contraceptive failure.

Substances diminishing the efficacy of COCs (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. cytochrome P450 enzymes, CYP34A, phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly also oxcarbazepine,
topiramate, felbamate, griseofulvin and herbal medicines containing St John's Wort (hypericum perforatum)).

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

Women prescribed any of these medicines should temporarily use a barrier method in addition Femme-Tab 20/100 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.

**Antibiotics (interference with enterohepatic circulation)**

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

Women prescribed antibiotics (except rifampicin and griseofulvin) should use a barrier method until 7 days after completing a course of antibiotics. If the period in which the barrier method is used runs beyond the end of the tablets in the Femme-Tab 20/100 pack, the next Femme-Tab 20/100 pack should be started without the usual tablet free interval.

Women taking interacting medications on a chronic basis should consider another method of contraception.

**Influence of Femme-Tab 20/100 on other medication**

Oral contraceptives may interfere with the metabolism of other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

The prescribing information of concomitant medications should be consulted to identify potential interactions.

**Effect on 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.

**Adverse Effects**

Various adverse effects have been associated with oral contraceptive use. The most serious effects associated with the use of oral contraceptives are discussed under “Precautions”.

In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide on whether Femme-Tab 20/100 use should be discontinued.
Clinical Trial Data

The table below displays the adverse events reported amongst patients in a clinical trial of levonorgestrel 100 µg/ethinyloestradiol 20 µg formulation, for contraception (n = 805). It includes all adverse events reported with an incidence of 1% or greater. A total of 8.4% of women discontinued the COC therapy due to the adverse events. Intermenstrual bleeding and metrorrhagia (4%) were the study events most frequently reported as the reason for discontinuing the COC therapy. All other events that resulted in discontinuation were reported by less than 1% of the women.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of women affected</th>
<th>Percent of women affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>63</td>
<td>7.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>31</td>
<td>3.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>9</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>142</td>
<td>17.6</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>58</td>
<td>7.2</td>
</tr>
<tr>
<td>Migraine</td>
<td>47</td>
<td>5.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>40</td>
<td>5.0</td>
</tr>
<tr>
<td>Increased libido</td>
<td>29</td>
<td>3.6</td>
</tr>
<tr>
<td>Depression</td>
<td>22</td>
<td>2.7</td>
</tr>
<tr>
<td>Nervousness</td>
<td>17</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Reproductive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast pain</td>
<td>90</td>
<td>11.2</td>
</tr>
<tr>
<td>Intermenstrual bleeding/metrorrhagia</td>
<td>35</td>
<td>4.3</td>
</tr>
<tr>
<td>Breast tension</td>
<td>11</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>62</td>
<td>7.7</td>
</tr>
</tbody>
</table>

A bioavailability study (n = 22) reported the following adverse events with a frequency of > 1%; intermenstrual bleeding 45%, headache/migraine 27%, dysmenorrhoea 23%, flu syndrome 18%, nausea 14%. A pharmacokinetic study (n = 18) reported the following adverse events with a frequency of > 1%; headache 78%, dysmenorrhoea 61%, flu syndrome 33%, common cold 28%, breast pain 17%.

Post-Marketing Data

The following adverse events have been reported in users of low dose oral contraceptives and have observed at the frequencies listed below, but an association has neither been confirmed nor totally refuted:

- **Very common**: > 1 in 10 (>10%)
- **Common**: > 1 in 100 and < 1 in 10 (between 1% and 10%)
- **Uncommon**: > 1 in 1000 and < 1 in 100 (between 0.1% and 1%)
- **Rare**: > 1 in 10000 and < 1 in 1000 (between 0.01% and 0.1%)
- **Very rare**: < 1 in 10000 (<0.01%)
<table>
<thead>
<tr>
<th>System/Organ/Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections &amp; infestations</td>
<td>Vaginitis (candidiasis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
<td>Aggravation of varicose veins</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, abdominal pain</td>
<td>Abdominal cramps, bloating, diarrhoea</td>
<td></td>
<td>Pancreatitis, hepatic adenomas, hepatocellular carcinomas</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td></td>
<td></td>
<td></td>
<td>Cholestatic jaundice</td>
<td>Gallbladder disease (including gallstones*)</td>
</tr>
<tr>
<td>Metabolism/nutrition</td>
<td>Changes in appetite (increase or decrease)</td>
<td>Glucose intolerance</td>
<td></td>
<td>Exacerbation of porphyria</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Mood changes including depression, changes in libido</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nervous</td>
<td>Headache including migraines</td>
<td>Nervousness, dizziness</td>
<td></td>
<td>Exacerbation of chorea</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Acne</td>
<td>Rash, urticaria, chloasma (melasma), which may persist, hirsutism, alopecia</td>
<td>Erythema nodosum</td>
<td>Erythema multiforme</td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td></td>
<td></td>
<td></td>
<td>Intolerance to contact lenses</td>
<td>Optic neuritis***, retinal vascular thrombosis</td>
</tr>
<tr>
<td>Reproductive system and breast</td>
<td>Metrorrhagia (breakthrough bleeding &amp; spotting)</td>
<td>Breast pain, tenderness, enlargement, secretion, dysmenorrhoea, change in menstrual flow, change in cervical ectropion &amp; secretion, vaginitis amenorrhoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary</td>
<td></td>
<td></td>
<td></td>
<td>Haemolytic uraemic syndrome</td>
<td></td>
</tr>
<tr>
<td>Immune</td>
<td></td>
<td></td>
<td></td>
<td>Anaphylactoid reactions including very rare cases of urticaria, angioedema, and severe reactions with respiratory &amp; circulatory symptoms</td>
<td>Exacerbation of systemic lupus erythematosus</td>
</tr>
<tr>
<td>General and</td>
<td>Fluid retention/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>administration site reactions</td>
<td>oedema</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>-------------------------------</td>
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<td>--------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Changes in weight (increase or decrease)</td>
<td>Increase in blood pressure, changes in serum lipid levels, including hypertriglyceridaemia</td>
<td>Decrease in serum folate levels**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Oral contraceptives may worsen existing gall bladder disease and may accelerate the development of this disease in previously asymptomatic women.
** Serum folate levels may be depressed by oral contraceptive therapy
*** Optic neuritis may lead to partial or complete loss of vision

In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.
Dose and Administration

Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year. The failure rate may increase when pills are missed or taken incorrectly.

How to Take Femme-Tab 20/100

One tablet is to be taken daily. Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. Tablet-taking is continuous for 21 consecutive days. Start with a tablet marked with the corresponding day of the week. Thereafter, one tablet is taken daily, following the arrows marked on the pack, until all tablets are taken.

The woman should be instructed to have a tablet free break of one week. Each subsequent pack is to be started immediately following the 7-day break. During the tablet free period a withdrawal bleed usually occurs. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

How to Start Femme-Tab 20/100

No preceding hormonal contraceptive use (in the past month)

Tablet taking should start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Femme-Tab 20/100 is effective from the first day of therapy if the tablets are begun as described above. Starting on days 2 - 5 of the menstrual cycle is allowed, but during the first cycle an additional barrier contraceptive method is recommended for the first 7 days of tablet taking.

Changing from another combined oral contraceptive (COC), or vaginal ring

The woman should start with Femme-Tab 20/100 preferably on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC.

Where a vaginal ring has been used, the woman should start using Femme-Tab 20/100 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 progestogen-releasing intrauterine system (IUS)

The woman may switch any day from the minipill, from an implant or IUS on the day of its removal, or from an injectable when the next injection would be due. In all of these cases, the woman should be advised to additionally use a barrier contraceptive method for the first 7 days of tablet taking.

Following first-trimester abortion

The woman may start tablet-taking immediately. When doing so, she need not take additional contraceptive measures.
Following delivery or second-trimester abortion

The woman should be advised to start on day 21 to 28 after delivery or second-trimester abortion. When starting later than day 28, the woman should be advised to additionally use a barrier contraceptive method for the first 7 days of tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before starting Femme-Tab 20/100 or the woman has to wait for her first menstrual period.

For breastfeeding women see “Use in lactation”

Additional contraceptive precautions

When additional contraceptive precautions are required the woman should be advised either to abstain from sex, or to use a barrier method of contraception, such as a cap (or diaphragm) plus spermicide, or for her partner to use a condom. Rhythm methods should not be advised as the COC disrupts the cyclical changes associated with the natural menstrual cycle e.g. changes in temperature and cervical mucus.

How to shift periods or how to delay a period

To delay a period the woman should continue with another pack of Femme-Tab 20/100 without having a tablet free interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of Femme-Tab 20/100 is then resumed after the usual 7-day tablet free interval.

To shift her period to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming tablet free interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough bleeding and spotting during the second pack (just as when delaying a period).

How to manage reduced reliability

When Femme-Tab 20/100 is taken according to the directions for use, the occurrence of pregnancy is highly unlikely. However, the reliability of oral contraceptives may be reduced under the following circumstances:

Management of Missed Tablets

If the user is less than 12 hours late in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take subsequent 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:

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

Accordingly the following advice can be given in daily practice:
Week 1

If the user is more than 12 hours late in taking any tablet (or several tablets) from the pack, she should take the last missed tablet as soon as she remembers, even if this means taking two tablets in one day at the same time, and then continue to take tablets at the normal time. Additional contraceptive precautions 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 are missed and the closer they are to the regular tablet-free interval, the higher the risk of a pregnancy.

Week 2

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 user 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 one tablet, the user should be advised to use extra precautions for 7 days.

Week 3

The risk of reduced reliability is imminent because of the forthcoming tablet-free interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the user has taken all tablets correctly. If this is not the case, the user should be advised to follow the first of these two options and to 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. The next pack must be started as soon as the current pack is finished, i.e. no gap should be left between packs. The user is unlikely to have a withdrawal bleed until the end of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. The user may also be advised to discontinue tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

If the user missed tablets and subsequently has no withdrawal bleed in the first normal tablet-free interval, the possibility of a pregnancy should be considered.

Advice in Case of Gastro-intestinal Disturbances

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

If vomiting or severe diarrhoea occurs within 3 - 4 hours after taking a tablet, the advice concerning 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.

**Overdosage**

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

**Symptoms**

Symptoms that may occur in case of taking an overdose of ‘active tablets’ are: nausea, vomiting and, in young girls, slight vaginal bleeding.

**Treatment**

There are no antidotes and further treatment should be symptomatic.

**Presentation and Storage Conditions**

Femme-Tab 20/100 tablets are contained in blister packs. Each blister pack contains 21 round white to off-white tablets containing ethinyloestradiol 20µg and levonorgestrel 100µg.

Femme-Tab 20/100 tablets are available in packs of 1 (sample pack), 3 and 4 blister packs. AUST R 170387

Store below 25°C. Protect from light and moisture. Keep in the original packaging. Store all medicines properly and keep them out of reach of children.

**Name and Address of the Sponsor**

AFT Pharmaceuticals Pty. Ltd. Level 1, 296 Burns Bay Rd Lane Cove SYDNEY NSW 2066 AUSTRALIA

**Poison Schedule of the Medicine**

S4 Prescription Medicine

**Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)**

10 January 2012
Date of most recent amendment
3 December 2012