

NEW ZEALAND DATA SHEET

1. FEMME-TAB ED 20/100

FEMME-TAB ED 20/100 Ethinylloestradiol 20 µg/Levonorgestrel 100 µg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each memo-pack contains 21 white active tablets and 7 red-brown placebo tablets.

Each active tablet contains ethinylloestradiol 20 µg and levonorgestrel 100 µg.

Each placebo tablet contains no active ingredient.

Excipients with known effect:

Lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Active tablets: white to off-white, round, convex, film-coated tablets.

Placebo tablets: red-brown, round, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

4.2 Dose and method of administration

Combined oral contraceptives (COCs), such as FEMME-TAB ED 20/100, 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 ED 20/100

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

How to start FEMME-TAB ED 20/100

START WITH THE FIRST TABLET FROM THE RED SECTION MARKED WITH THAT DAY OF THE WEEK, in accordance with one of the following:

- *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 - 3 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), vaginal ring or transdermal patch:*

The woman should start with FEMME-TAB ED 20/100 preferably on the day after the last hormonal tablet of her previous COC, but at the latest on the day following the usual tablet-free or non-hormonal tablet interval of her previous COC.

In case a vaginal ring or transdermal patch has been used, the woman should start using FEMME-TAB ED 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 immediately. When doing so, she need not take additional contraceptive measures.

- *Following delivery or second-trimester abortion:*

The woman should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later than this, 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 ED 20/100 or the woman has to wait for her first menstrual period.

Management of missed tablets

Errors in taking the non-hormonal tablets contained in FEMME-TAB ED 20/100 can be ignored. However, they should be discarded to avoid unintentionally prolonging the placebo tablet phase. The following advice only refers to missed hormonal tablets:

If the user is **less than 12 hours** late in taking any hormonal 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 a tablet, contraceptive protection may be reduced.

There is a particularly high risk of pregnancy if tablets are missed just before or immediately after taking the non-hormonal tablets. If tablets are missed in the first week of taking hormonal tablets following the non-hormonal tablets and intercourse took place in the preceding 7 days, the possibility of pregnancy should be considered.

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.

These rules form the basis of the instructions to patients provided in the package insert.

Extra contraceptive precautions

When you need extra contraceptive precautions, either:

- don't have sex; or
- use a cap plus spermicide; or
- use a condom

Do not use the rhythm or temperature methods as extra contraceptive precautions. This is because oral contraceptives alter the usual menstrual cycle changes such as changes in temperature and cervical mucus.

The 7 day rule

- Continue taking your Pills.
- You will not be protected from pregnancy until you have taken your daily small hormone Pill for the next 7 days in a row
- Use another method of contraception (Extra contraceptive precautions) such as condoms or do not have sexual intercourse for the next 7 days
- If there are fewer than 7 small hormone Pills left in the pack, or before the large non-hormonal Pills in the pack, go straight on to the Pills in the red section of the next pack. This means that you miss out the large non-hormone Pills. You may not have a period until the end of the next pack. This is not harmful.

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

Advice in case of vomiting or severe diarrhoea

If vomiting or severe diarrhoea occurs within 3-4 hours after hormonal tablet taking, absorption may not be complete and additional barrier contraceptive measures should be used. In such an event, the advice concerning 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 shift periods or how to delay a period

To delay a period the woman should continue with hormonal tablets from another pack of FEMME-TAB ED 20/100 without taking the non-hormonal tablets from her current pack. The extension can be carried on for as long as desired until the end of the hormonal tablets in the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of FEMME-TAB ED 20/100 is then resumed after the non-hormonal tablet phase.

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming non-hormonal tablet phase by as many days as she likes. The shorter the hormone-free 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).

4.3 Contraindications

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 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
- Disturbed lipometabolism
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see also section 4.4, Circulatory Disorders).
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumors (benign or malignant)
- History of migraine with focal neurological symptoms
- 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 any of the active substances or excipients of FEMME-TAB ED 20/100
- FEMME-TAB ED 20/100 is contraindicated for use with the Hepatitis C combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin (see section 4.4).

4.4 Special warnings and precautions for use

The clinical and epidemiological evidence for COCs like FEMME-TAB ED 20/100 is predominantly based on experience with COCs in general. Therefore, the following warnings related to the use of COCs apply also to the use of FEMME-TAB ED 20/100.

If any of the conditions/risk factors mentioned below are present, the benefits of COC 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 whether the COC 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, stroke, deep venous thrombosis, and pulmonary embolism. 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 ever uses a COC. The approximate incidence of VTE in users of low estrogen dose (< 0.05 mg ethinylestradiol) OCs is up to 4 per 10 000 woman years compared to 0.5 - 3 per 10 000 woman years in non-OC users. However, the incidence of VTE occurring during COC use is substantially less than the incidence associated with pregnancy (i.e. 6 per 10 000 pregnant woman years).

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 or arterial thrombotic/thromboembolic events or of cerebrovascular accident 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 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 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)
- dyslipoproteinemia
- 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 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 section 4.6).

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 headaches during COC use, in particular the onset of migraine 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 ethinylestradiol).

Tumors

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, and even more rarely, malignant liver tumors have been reported in users of COCs. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.

Hepatitis C

During clinical trials with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin, transient, asymptomatic elevations of alanine transaminase (ALT) greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylloestradiol-containing medications such as combined oral contraceptives, contraceptive patches, or contraceptive vaginal rings.

FEMME-TAB ED 20/100 must be discontinued 2 weeks prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin. FEMME-TAB ED 20/100 can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

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; hemolytic 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 < 0.05 mg ethinylestradiol). 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.

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstatement of FEMME-TAB ED 20/100, guided by the contraindications in section 4.3 and the warnings and precautions in section 4.4. This should be repeated at least annually during the use of FEMME-TAB ED 20/100. 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 FEMME-TAB ED 20/100. 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.

Women should be advised that preparations like FEMME-TAB ED 20/100 do not protect against HIV infections (AIDS) and other sexually transmissible diseases.

Reduced efficacy

The efficacy of FEMME-TAB ED 20/100 may be reduced in the event of missed hormonal tablets (see section 4.2), vomiting or severe diarrhea (see section 4.2) or concomitant medication (see section 4.5).

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 while taking the 7 non-hormonal tablets. If the COC has been taken according to the directions described in section 4.2, it is unlikely that the woman is pregnant. However, if the COC 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 COC use is continued.

4.5 Interaction with other medicines and other forms of interaction

Interactions between oral contraceptives and other medicines which result in an increased clearance of sex hormones can lead to breakthrough bleeding and/or oral 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 the 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 estrogens may decrease when certain antibiotic agents are given, which may reduce ethinylestradiol concentrations (e.g. penicillins and tetracyclines).

Women on short-term treatment with any of the above-mentioned classes of medicines or individual medicines, should temporarily use a barrier method in addition to taking hormonal FEMME-TAB ED 20/100 tablets, i.e. during the time of concomitant medicine administration and for 7 days after their discontinuation. For women on rifampicin or other microsomal enzyme-inducing medicines, a barrier method should be used in addition to FEMME-TAB ED 20/100 during the time of concomitant medicine administration and for 28 days after its discontinuation. Women on treatment with antibiotics (except rifampicin and griseofulvin) should use a barrier method until 7 days after discontinuation. If the period during which the barrier method is used runs beyond the end of the hormonal tablets in the FEMME-TAB ED 20/100 pack, the non-hormonal tablets should be omitted and the next FEMME-TAB ED 20/100 pack should be started.

Oral contraceptives such as FEMME-TAB ED 20/100 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.

Laboratory tests

The use of preparations like FEMME-TAB ED 20/100 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The administration of FEMME-TAB ED 20/100 is contraindicated during pregnancy. If pregnancy occurs during treatment with FEMME-TAB ED 20/100, further intake should be stopped.

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).

Extensive epidemiological studies have revealed neither an increased risk of birth defects 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 section 4.3.

Breast-feeding

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore the use of COCs 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.

4.7 Effects on ability to drive and use machines

FEMME-TAB ED 20/100 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Serious undesirable effects of FEMME-TAB ED 20/100 have been referred to in sections 4.3 and 4.4.

In addition, the following undesirable effects have been reported in users of COCs such as FEMME-TAB ED 20/100, although the causal relationships have not been confirmed:

System Organ Class	Common ($\geq 1/100$)	Uncommon ($\geq 1/1000$ and $< 1/100$)	Rare ($< 1/1000$)
Eye Disorders			Contact lens intolerance
Gastrointestinal Disorders	Nausea, abdominal pain	Vomiting, diarrhoea	
Immune System Disorders			Hypersensitivity
Investigations	Weight increase		Weight decrease
Metabolism and Nutrition Disorders		Fluid retention	
Nervous System Disorders	Headache	Migraine	
Psychiatric Disorders	Depressed mood, altered mood	Increased libido	Decreased libido
Reproductive System and Breast Disorders	Breast pain, breast tenderness	Breast hypertrophy	Vaginal discharge, breast discharge
Skin and Subcutaneous Tissue Disorders		Rash, urticaria	Erythema nodosum, erythema multiforme

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions: <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The contraceptive effect of FEMME-TAB ED 20/100 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. When FEMME-TAB ED 20/100 is taken according to instructions, the egg cells are prevented from maturing to the point at which they can be fertilised, the cervical mucus remains thick so as to constitute a barrier to sperm, and the endometrium is rendered unreceptive to implantation.

As well as protection against pregnancy, estrogen/progestogen combinations have several positive properties which, next to the negative properties (see sections 4.4 and 4.8), can be useful in deciding on the method of birth control.

With combined oral contraceptives (COCs) the cycle is more regular and menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. Apart from this there is evidence of a reduced risk of endometrial cancer and ovarian cancer. With the higher-dosed combined oral contraceptives containing 0.05 mg ethinylloestradiol, there is evidence of a reduced risk of fibrocystic tumors of the breasts, ovarian cysts, pelvic inflammatory disease and ectopic pregnancy. This may also apply to lower-dosed COCs.

5.2 Pharmacokinetic properties

Levonorgestrel

Absorption

Orally administered levonorgestrel is rapidly and completely absorbed. Peak serum concentrations of 2.3 ng/mL are reached 1.3 hours after single ingestion.

Levonorgestrel is almost completely bioavailable after oral administration.

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 and about 34% non-specifically bound to albumin. The ethinylestradiol-induced increase in SHBG influences the proportion of levonorgestrel bound to 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 levonorgestrel is 129 L after single administration.

Metabolism

Levonorgestrel is completely metabolized by known pathways of steroid metabolism. The metabolic clearance rate from serum is approximately 1.0 mL/min/kg.

Elimination

Levonorgestrel serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 25 hours. Levonorgestrel is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1:1. The half-life of metabolite excretion is about 1 day.

Steady-state conditions

Following daily ingestion, medicine serum levels increase about three-fold reaching steady-state conditions during the second half of the treatment cycle.

Levonorgestrel pharmacokinetics are influenced by SHBG levels, which are increased 1.5-1.6 fold when co-administered with ethinylestradiol. At steady-state, clearance rate and volume of distribution are slightly reduced to 0.7 mL/min/kg and about 100 L, respectively.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 50 pg/mL are reached within 1-2 hours. During absorption and first-pass liver passage, ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of about 45% with a large interindividual variation of about 20-65%.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approx. 98%), and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 2.8-8.6 L/kg was reported.

Metabolism

Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized 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 sulfate. The metabolic clearance rate was reported to be 2.3-7 mL/min/kg.

Elimination

Ethinylestradiol serum levels decrease in two disposition phases characterized by half-lives of about 1 hour and 10-20 hours, respectively. Unchanged medicine 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

Ethinylestradiol serum concentrations increase about two-fold after daily oral administration of FEMME-TAB ED 20/100. According to the variable half-life of the terminal disposition phase from serum and the daily ingestion, steady-state serum levels of ethinylestradiol will be reached after about

one week.

5.3 Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumors.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Hypromellose
Iron oxide red
Lactose monohydrate
Macrogol 4000
Magnesium stearate
Maize starch
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

FEMME-TAB ED 20/100 is packaged in PVC/PVDC/aluminium blister strips of 21 active tablets and 7 placebo tablets, supplied in a carton of 112 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

AFT Pharmaceuticals Ltd
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Phone: 0800 423 823
Email: customer.service@aftp pharm.com

9. DATE OF FIRST APPROVAL

17/07/2019

10. DATE OF REVISION OF THE TEXT

None.