PROFESSIONAL INFORMATION FOR NESSIFEM

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

NESSIFEM 60 µg / 15 µg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The 28-day pack (Every-day calendar pack) contains 24 active hormonal yellow film-coated tablets plus 4 inactive non-hormonal (placebo) white tablets.

Each active yellow film-coated tablet contains gestodene 60 µg and ethinylestradiol 15 µg.

The inactive white tablets are placebo and do not contain any active ingredients.

Contains sugar: each active yellow film-coated tablet contains 57,61 mg lactose monohydrate and each inactive white tablet contains 70,70 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Active film-coated tablets

24 yellow, round, plain film-coated tablets, with a diameter of 5,5 mm approximately.

Inactive tablets (placebo)

4 white, round, biconvex, plain tablets, with a diameter of 5,5 mm approximately.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NESSIFEM is indicated for the prevention of pregnancy (oral contraception).

4.2 Posology and method of administration

The 24 yellow tablets contain active ingredients (active tablets).

The 4 white tablets do not contain any active ingredients (inactive tablets).

To achieve maximum contraceptive effectiveness, NESSIFEM must be taken at the same time every day, preferably after the evening meal or at bedtime.

The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. "MO" for Monday).

Following the directions shown by the arrows, one tablet must be taken daily, for 28 consecutive days, until the pack is finished.

Each subsequent pack is started on the day after the last tablet of the previous pack.

A withdrawal bleed usually starts on days 2 - 3, after the last active tablet and may not have finished before the next pack is started. The tablets are taken daily and pack follows pack without interruption and without regard to bleeding.

How to start NESSIFEM:

No preceding hormonal contraceptive use (in the past month):

Tablet taking has to start on day 1 of the woman's natural menstrual cycle (i.e. the first day of her menstrual bleeding).

The first tablet must be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. "MO" for Monday).

Then take 1 tablet every day following the directions shown by the arrows.

Starting on days 2 - 7 of the menstrual cycle is allowed, but for the first 7 days of tablet-taking during the first cycle, a non-hormonal backup method of birth control (such as condoms and spermicide) is recommended. Thereafter, one tablet is taken daily, following the arrows on the package, until all 28 tablets have been taken.

Changing from another Combination Oral Contraceptive (COC) to NESSIFEM:

The woman should start NESSIFEM preferably on the day after the last active tablet of her previous combination oral contraceptive, but at the latest, on the day following the usual tablet-free or inactive tablet interval of her previous combination oral contraceptive.

The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. "MO' for Monday). Then take 1 tablet every day following the directions shown by the arrows.

Changing from a progestogen-only method (progestogen-only pill, injection, implant):

The woman may switch any day from the progestogen-only pill and should begin NESSIFEM the next day. She should start NESSIFEM on the day of an implant removal or, if using an injection, the day the next injection would be due. In all of these situations, the woman should be advised to use a non-hormonal backup method for the first 7 days of tablet-taking.

The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. “MO’ for Monday). Then take 1 tablet every day following the directions shown by the arrows.

Following first-trimester abortion:

The woman may start NESSIFEM immediately. Additional contraceptive measures are not needed.

The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. “MO’ for Monday). Then take 1 tablet every day following the directions shown by the arrows.

Following delivery or second-trimester abortion:

Since the immediate post-partum period is associated with an increased risk of thromboembolism, NESSIFEM should be started no earlier than day 28 after delivery in the non-lactating mother or after second-trimester abortion. The woman should be advised to use a non-hormonal backup method for the first 7 days of tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of NESSIFEM use or the woman must wait for her first menstrual period. See section 4.4

The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. “MO’ for Monday). Then take 1 tablet every day following the directions shown by the arrows.

Management of missed tablets:

Contraceptive protection may be reduced if active (yellow) tablets are missed and particularly if the missed tablets extend the inactive (white) tablet interval.

- If one active tablet is missed, but is **less than 12 hours** late, it should be taken as soon as it is remembered. Subsequent tablets should be taken at the usual time.
- If one active tablet is missed and is **more than 12 hours** late or if more than one active tablet is missed, contraceptive protection may be reduced. The last missed tablet should be taken as soon as it is remembered, even if this means taking two tablets in one day. Subsequent tablets should be taken at the usual time. In addition, a non-hormonal backup method of birth control should be used for the next seven days.
- If the seven days where backup is required run beyond the last active tablet in the current pack, the next pack must be started on the day following the intake of the last active tablet in the current pack; all inactive tablets should be discarded. This prevents an extended break in tablet-taking of active tablets that may increase the risk of escape ovulation. The user is unlikely to have a withdrawal bleed until the inactive-tablet interval of the second pack but she may experience spotting or breakthrough bleeding on days when active tablets are taken.
- If the user does not have a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be ruled out before resuming tablet-taking.

Advice in case of gastrointestinal disturbance:

If vomiting or severe diarrhoea occurs within 4 hours after tablet-taking, absorption may not be complete. In such an event, the advice concerning "Management of missed tablets" is applicable. The woman must take the extra active tablet(s) needed from a backup pack.

How to delay a period:

To delay a period the woman should continue with another pack of NESSIFEM without the inactive-tablet interval. The extension can be continued until the end of the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of NESSIFEM is then resumed after the usual 4-day inactive tablet interval.

Additional information on special populations:

Children and adolescents:

NESSIFEM is only indicated after menarche.

Elderly population:

NESSIFEM is not indicated after menopause.

Patients with hepatic impairment:

NESSIFEM is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal. See section 4.3.

Patients with renal impairment:

NESSIFEM has not been studied in patients with renal impairment.

Method of administration:

NESSIFEM tablets are for oral administration with a drink of water.

4.3 Contraindications

Hypersensitivity to gestodene or ethinylestradiol, or to any of the excipients of NESSIFEM listed in section 6.1.

NESSIFEM is contraindicated in patients with:

- Deep vein thrombosis (current or history);
- thromboembolism (current or history);
- cerebrovascular or coronary artery disease;
- thrombogenic valvulopathies;
- thrombogenic rhythm disorders;
- hereditary or acquired thrombophilias;
- headache with focal neurological symptoms, such as aura;
- diabetes with vascular involvement;
- uncontrolled hypertension; (See section 4.4);
- known or suspected carcinoma of breast, or other known or suspected oestrogen-dependent neoplasias;
- hepatic adenomas or carcinomas, or active liver disease as long as liver function values have not returned to normal;
- undiagnosed vaginal bleeding;
- known or suspected pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Cigarette smoking increases the risk of serious cardiovascular adverse reactions from oral contraceptive use. This risk increases with age and the extent of smoking (15 or more cigarettes per day was associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use NESSIFEM should be strongly advised not to smoke.

Venous and arterial thrombosis and thromboembolism

Use of NESSIFEM is associated with an increased risk of venous and arterial thrombotic and thromboembolic events.

Minimising exposure to oestrogens and progestins is in keeping with good principles of therapeutics. For any particular oestrogen/progestin combination, the dosage regimen prescribed should be one that contains the least amount of oestrogen and progestin that is compatible with a low failure rate and the needs of the individual patient. New acceptors of combination oral contraceptives should be started on preparations containing less than 50 µg of oestrogen.

Venous thrombosis and thromboembolism

Use of NESSIFEM increases the risk of venous thrombotic and thromboembolic events. Reported events include deep venous thrombosis and pulmonary embolism. For information on retinal vascular thrombosis see "Ocular lesions".

The increased risk is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is less than the risk of venous thrombotic and thromboembolic events associated with pregnancy which is estimated as 60 cases per 100 000 women-years. Venous thromboembolism is fatal in 1 - 2 % of cases.

In several epidemiological studies it has been found that women using combined oral contraceptives with ethinylestradiol, mostly with a dose of 30 µg, and a progestin such as gestodene have an increased risk of venous thrombotic and thromboembolic events compared with those using COCs containing less than 50 µg of ethinylestradiol and the progestin levonorgestrel. Data from some additional studies have not shown this increase in risk.

For COCs containing gestodene with 15 µg of ethinylestradiol (such as NESSIFEM) there are no data on the comparative risk of venous thrombotic and thromboembolic events. For COCs containing 30 µg of ethinylestradiol combined with desogestrel or gestodene compared with those containing less than 50 µg of

ethinylestradiol and levonorgestrel, the overall relative risk of venous thrombotic and thromboembolic events has been estimated to range between 1,5 and 2,0. The incidence of venous thrombotic and thromboembolic events for levonorgestrel containing COCs with less than 50 µg of ethinylestradiol is approximately 20 cases per 100 000 woman-years of use. For COCs containing 30 µg of ethinylestradiol combined with desogestrel or gestodene the incidence is approximately 30 - 40 cases per 100 000 woman-years of use, i.e. additional 10 - 20 cases per 100 000 women-years of use.

The risk of venous thrombotic or thromboembolic events is further increased in women with conditions predisposing for venous thrombosis and thromboembolism. Caution must be exercised when prescribing NESSIFEM for such women.

Examples of predisposing conditions for venous thrombosis and thromboembolism are:

- Obesity;
- surgery or trauma with increased risk of thrombosis;
- recent delivery or second-trimester abortion;
- prolonged immobilisation;
- increasing age.

Further risk factors, which represent contraindications for the use of NESSIFEM, are listed in section 4.3.
The relative risk of postoperative thromboembolic complications has been reported to be increased two-to four-fold with the use of combination oral contraceptives. The relative risk of venous thrombosis in women with predisposing conditions is twice that of women without such conditions. If feasible, NESSIFEM should be discontinued:

- for four weeks prior to and for two weeks after elective surgery with increased risk of thrombosis, and;
- during prolonged immobilisation.

Since the immediate post-partum period is associated with an increased risk of thromboembolism, NESSIFEM should be started no earlier than day 28 after delivery or second-trimester abortion (See section 4.6).

Arterial thrombosis and thromboembolism

The use of NESSIFEM increases the risk of arterial thrombotic and thromboembolic events.

Reported events include myocardial infarction and cerebrovascular events (ischaemic and haemorrhagic stroke, transient ischaemic attack). For information on retinal vascular thrombosis see "Ocular lesions".
The risk of arterial thrombotic and thromboembolic events is further increased in women with underlying risk factors.
Caution must be exercised when prescribing NESSIFEM for women with risk factors for arterial thrombotic and thromboembolic events.

Examples of risk factors for arterial thrombotic and thromboembolic events are:

- Smoking;
- hypertension;
- hyperlipidaemias;
- obesity;
- increasing age.

NESSIFEM users with migraine (particularly migraine with aura) may be at increased risk of stroke.
Further risk factors, which represent contraindications for the use of NESSIFEM, are listed in section 4.3.

Ocular lesions

With use of medicines like NESSIFEM, there have been reports of retinal vascular thrombosis, which may lead to partial or complete loss of vision. If there are signs or symptoms such as visual changes, onset of proptosis or diplopia, papilledema, or retinal vascular lesions, NESSIFEM should be discontinued and the cause immediately evaluated.

Blood pressure

Increases in blood pressure have been reported in women taking medicines like NESSIFEM. In women with hypertension, a history of hypertension or hypertension related diseases (including certain renal diseases); another method of contraception may be preferable. If NESSIFEM is used in such cases, close monitoring is recommended and, if a significant increase in blood pressure occurs, NESSIFEM should be discontinued.
Elevated blood pressure associated with NESSIFEM use will generally return to baseline after stopping NESSIFEM and there appears to be no difference in the occurrence of hypertension among ever- and never-users.

NESSIFEM use is contraindicated in women with uncontrolled hypertension (see section 4.3).

Carcinoma of the reproductive organs

Some studies suggest that combination oral contraceptive use, such as NESSIFEM, may be associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women.

However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behaviour and other factors. In cases of undiagnosed abnormal genital bleeding, adequate diagnostic measures are indicated.

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 using combination oral contraceptives compared to never-users. The increased risk gradually disappears during the course of the 10 years after cessation of combination oral contraceptive use. These studies do not provide evidence for causation. The observed pattern of increased risk of breast cancer diagnosis may be due to earlier detection of breast cancer in combination oral contraceptive users (due to more regular clinical monitoring), the biological effects of combination oral contraceptives, or a combination of both. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent combination oral contraceptive users is small in relation to the lifetime risk of breast cancer. Breast cancers diagnosed in ever-users tend to be less advanced clinically that the cancers diagnosed in never-users.

Hepatic neoplasms / Liver disease

In some cases, hepatic adenomas or hepatocellular carcinoma may be associated with combination oral contraceptive (COC) use such as NESSIFEM. The risk appears to increase with duration of oral contraceptive use. Rupture of hepatic adenomas may cause death through intra-abdominal haemorrhage. Women with a history of oral contraceptive related cholestasis or women with cholestasis during pregnancy are more likely to have this condition with combination oral contraceptive use such as NESSIFEM.

If these patients receive NESSIFEM they should be carefully monitored and, if the condition recurs, NESSIFEM should be discontinued.

Migraine/ Headache

The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent or severe requires discontinuation of NESSIFEM and evaluation of the cause.

Women with migraine (particularly migraine with aura) who take NESSIFEM may be at increased risk of stroke.

Medical examinations

1. A complete personal and family medical history and physical examination, including blood pressure, should be taken prior to the initiation of NESSIFEM use. Such medical examinations should be repeated periodically during the use of NESSIFEM.
2. Optic neuritis may lead to partial or complete loss of vision.
3. Combination oral contraceptives such as NESSIFEM may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.
4. Serum folate levels may be depressed by combination oral contraceptive therapy such as NESSIFEM. This may be of clinical significance if the woman becomes pregnant shortly after discontinuing NESSIFEM.

Carbohydrate and lipid effects

Glucose intolerance has been reported in users of combination oral contraceptive such as NESSIFEM. Women with impaired glucose tolerance or diabetes mellitus who use NESSIFEM should be carefully monitored.

A small proportion of women will have adverse lipid changes while taking NESSIFEM. Non-hormonal contraception should be considered in women with uncontrolled dyslipidaemias.

Persistent hypertriglyceridemia may occur in a small proportion of NESSIFEM users. Elevations of plasma triglycerides may lead to pancreatitis and other complications.

Oestrogens increase serum high-density lipoproteins (HDL cholesterol), whereas a decline in serum HDL cholesterol has been reported with many progestational medicines. Some progestins may elevate low-density lipoprotein (LDL) levels and may render the control of hyperlipidaemias more difficult. The net effect of a combination oral contraceptive depends on the balance achieved between doses of oestrogen and progestin and the nature and absolute amount of progestins used in the contraceptive. The amount of both hormones should be considered in the choice of a combination oral contraceptive. Women who are being treated for hyperlipidaemias should be followed closely if they elect to use NESSIFEM.

Genital bleeding

In some women withdrawal bleeding may not occur during the inactive-tablet interval. If NESSIFEM has not been taken according to directions prior to the first missed withdrawal bleed, or if two consecutive withdrawal bleeds are missed, tablet-taking should be discontinued and a non-hormonal backup method of contraception should be used until the possibility of pregnancy is excluded.

Breakthrough bleeding/spotting may occur in women taking NESSIFEM, especially during the first three months of use. The type and dose of progestin may be important. If this bleeding persists or recurs, non-hormonal causes should be considered and adequate diagnostic measures may be indicated to rule out pregnancy, infection, malignancy or other conditions. If pathology has been excluded, continued use of NESSIFEM or a change to another formulation may solve the problem.

Some women may encounter post-pill amenorrhoea (possibly with anovulation) or oligomenorrhoea, especially when such a condition was pre-existent.

Depression

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Other

Patients should be counselled that this product does not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Diarrhoea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations. See section 4.2.

Lactose

NESSIFEM contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take NESSIFEM.

4.5 Interaction with other medicines and other forms of interaction

Interactions between ethinylestradiol (EE) and other substances may lead to decreased or increased serum EE concentrations, respectively.

Decreased EE serum concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of NESSIFEM.

During concomitant use of EE- containing products and substances that may lead to decreased EE serum concentrations, it is recommended that a non-hormonal backup method of birth control such as condoms and spermicide) be used in addition to the regular intake of NESSIFEM. In the case of prolonged use of such substances NESSIFEM should not be considered the primary contraceptive.

After discontinuation of substances that may lead to decreased EE serum concentrations, use of a non-hormonal backup method is recommended for at least 7 days. Longer use of a backup method is advisable after discontinuation of substances that have led to induction of hepatic microsomal enzymes, resulting in decreased EE serum concentrations. It may sometimes take several weeks until enzyme induction has completely subsided, depending on dosage, duration of use and rate of elimination of the inducing substance.

Examples of substances that may decrease serum EE concentrations:

- Any substance that reduces gastrointestinal transit time and, therefore, EE absorption;
- substances that induce hepatic microsomal enzymes, such as rifampicin, rifabutin, barbiturates, primidone, phenylbutazone, phenytoin, dexamethasone, griseofulvin, topiramate, some protease inhibitors, modafinil;
- *hypericum perforatum*, also known as St. John's wort, and ritonavir[1] (possibly by induction of hepatic microsomal enzymes);
- certain antibiotics (e.g. ampicillin and other penicillins, tetracyclines), by a decrease of enterohepatic circulation of oestrogens.

During treatment with any of these medicines, a barrier method such as a condom should be temporarily used in addition to NESSIFEM, or another method of contraception should be chosen if these medicines are going to be used for prolonged periods.

With microsomal enzyme-inducing medicines the barrier method should be used for the duration of the concomitant administration and for 28 days after discontinuation of the medicine. It may even take several weeks until enzyme induction has completely subsided.

Women treated with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after completing the course.

If the period during which the barrier method is used is longer than the pills in the NESSIFEM pack last, then the next pack of NESSIFEM should be started without respecting the usual interval in which no tablets are taken.

Examples of substances that may increase serum EE concentrations:

- Atorvastatin;
- competitive inhibitors for sulphation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and paracetamol;
- substances that inhibit cytochrome P450 3A4 isoenzyme such as indinavir, voriconazole, fluconazole and troleandomycin;[1]

Troleandomycin may increase the risk of intrahepatic cholestasis during co-administration with NESSIFEM.

EE may interfere with the metabolism of other medicines by:

- Inhibiting hepatic microsomal enzymes; or by
- inducing hepatic drug conjugation, particularly glucuronidation.

[1] Although ritonavir is an inhibitor of cytochrome P450 3A4, treatment with ritonavir has been shown to decrease EE serum concentration (see above), as it induces the metabolism other CYP isoenzymes and UGT. (M.D. 38th Ed. p 1013).

- Accordingly, plasma and tissue concentrations may either be increased (e.g. cyclosporine, theophylline, corticosteroids) or decreased (e.g. lamotrigine, levothyroxine, valproate).

In patients treated with flunarizine, use of NESSIFEM may increase the risk of galactorrhoea.

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

Interference with laboratory and other diagnostic tests:

Effects on laboratory parameters

The use of NESSIFEM may cause certain physiologic changes, which may be reflected in the results of certain laboratory tests, including:

- Biochemical parameters of liver function (including a decrease in bilirubin and alkaline phosphatase), thyroid function (increased total T3 and T4 due to increased TBG, decreased free T3 resin uptake), adrenal function (increased plasma cortisol, increased cortisol binding globulin, decreased dehydroepiandrosterone sulphate (DHEAS), and renal function (increased plasma creatinine and creatinine clearance);
- plasma levels of (carrier) proteins, such as corticosteroid-binding globulin and lip/lipoprotein fractions;
- parameters of carbohydrate metabolism;
- parameters of coagulation and fibrinolysis;
- decreased serum folate levels.

Pharmacodynamic interactions

Concomitant use of NESSIFEM and ARVs such as ribavirin and ritonavir combinations may increase the risk of ALT elevations.

4.6 Fertility, pregnancy and lactation

Pregnancy

NESSIFEM is contraindicated in pregnancy.

Extensive epidemiological studies have revealed no increased risk of birth defects in children born to women who used combination oral contraceptives prior to pregnancy.

Studies do not suggest a teratogenic effect; particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. (See section 4.3).

Breastfeeding

Small amounts of contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. Lactation may be influenced by NESSIFEM as it may reduce the quantity and change the composition of breast milk. The use of NESSIFEM is generally not recommended until the breastfeeding mother has completely weaned her child. Also see section 4.4 regarding postpartum use.

4.7 Effects on ability to drive and use machines

NESSIFEM may cause headache, dizziness and vertigo which may have an influence on the ability to drive and use machines. Patients should be advised to exercise caution until they know how NESSIFEM affects them.

4.8 Undesirable effects

Summary of the safety profile

An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using oral contraceptives such as NESSIFEM.

The occurrence of amenorrhea was reported in 15 % of women. Some most frequently (greater than 10 %) reported adverse events are headache, including migraines, abdominal pain, breast pain, breast tenderness.

For serious adverse effects also see section 4.4.

Adverse reactions

Adverse reactions and their frequencies are reported in Table 1 by system organ class and by frequency.

Table 1: Tabulated summary of adverse reactions

The following undesirable effects have been reported.

System Organ Class	**NESSIFEM Side Effects**
Infections and infestations	
Frequent:	Vaginitis, including candidiasis.
Neoplasm benign, malignant and unspecified (including cysts and polyps)	
Frequency unknown:	Hepatocellular carcinoma and benign hepatic tumours (e.g. focal nodular hyperplasia, hepatic adenoma).
Immune system disorders	
Frequency unknown:	Anaphylactic/anaphylactoid reaction, including angioedema, severe reactions with respiratory and circulatory symptoms and urticaria.

Metabolism and nutrition disorders	
Less frequent:	Increased appetite, decreased appetite.
Frequency unknown:	Glucose tolerance impaired.
Psychiatric disorders	
Frequent:	Mood changes, including depression, nervousness and changes in libido.
Frequency unknown:	Severe depression with a risk of suicidal thoughts/behaviour and suicide.
Nervous system disorders	
Frequent:	Dizziness, headache including migraines.
Frequency unknown:	Optic neuritis, chorea aggravated
Eye disorders	
Less frequent:	Retinal vascular thrombosis.
Frequency unknown:	Contact lens intolerance.
Vascular disorders	
Less frequent:	Aggravation of varicose veins, venous thromboembolism and arterial thromboembolism.
Gastrointestinal disorders	
Frequent:	Vomiting, nausea, bloating, abdominal pain.
Less frequent:	Pancreatitis.
Frequency unknown:	Ischaemic colitis and possible aggravation of inflammatory bowel disease.
Hepato-biliary disorders	
Less frequent:	Hepatic and hepatobiliary disorders (e.g. hepatitis, hepatic function abnormal), biliary

	lithiasis[1], gallbladder disease including gallstones[2].
Frequency unknown:	Cholestatic jaundice, cholestasis[1].
Skin and subcutaneous tissue disorders	
Frequent:	Acne, rash, alopecia.
Less frequent:	Chloasma, which may persist, hirsutism.
Frequency unknown:	Erythema multiforme, erythema nodosum.
Musculoskeletal and connective tissue disorders	
Frequency unknown:	Exacerbation of systemic lupus erythematosus.
Renal and urinary disorders	
Frequency unknown:	Haemolytic uremic syndrome.
Reproductive system and breast disorders	
Frequent:	Breakthrough bleeding, spotting, dysmenorrhoea, change in menstrual flow, change in cervical ectropion and secretion, amenorrhea, breast pain, breast tenderness.
Less frequent:	Breast secretion, breast enlargement.
Congenital, familial and genetic disorders	
Frequency unknown:	Exacerbation of porphyria.
General disorders and administration site conditions	
Frequent:	Fluid retention / oedema.
Investigations	
Frequent:	Increased weight, decreased weight.
Less frequent:	Increased in blood pressure, increase in lipids, decrease in serum folate levels.

[1] COCs such as NESSIFEM may worsen existing biliary lithiasis and cholestasis.

[2] COCs such as NESSIFEM may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of NESSIFEM is important. It allows continued monitoring of the benefit/risk balance of NESSIFEM. Healthcare professionals are asked to report any suspected adverse reactions. Suspected adverse reactions can be reported to Cipla Medpro (Pty) Ltd at drugsafetysa@cipla.com or telephone 080 222 6662 (toll free). Suspected adverse reactions can also be reported to SAHPRA via the"Med Safety APP" (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms of NESSIFEM overdosage may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding, may occur in females. There is no specific antidote and further treatment of overdose, if necessary, is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 18.8 Ovulation controlling agents

NESSIFEM is a low-dose monophasic ovulation-controlling medicine with oestrogenic and progestogenic peripheral effects.

The mode of action of gestodene in combination with ethinylestradiol includes the inhibition of ovulation by suppression of the mid-cycle surge of luteinising hormone, suppression of endometrial development thus rendering the endometrium unreceptive to implantation and the thickening of cervical mucus so as to constitute a barrier to sperm.

5.2 Pharmacokinetic properties

Gestodene

Absorption

Orally administered gestodene is well absorbed. Peak serum concentration of approximately 2-4 ng/ml is reached at about 1 hour after acute ingestion. Bioavailability is approximately 99 %.

Distribution

Gestodene is bound to serum albumin and to sex hormone binding globulin (SHBG).

Only 1 - 2 % of the total serum gestodene concentration is present as free steroid,

50 - 70 % is specifically bound to SHBG. The ethinylestradiol–induced increase in SHBG influences the proportion of gestodene 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 gestodene is 0,7 – 1,4 L/kg.

Metabolism

Gestodene is completely metabolised by the known pathways of steroid metabolism. The mean metabolic clearance rate from the serum is 0,8 – 1,0 ml/min/kg. When gestodene was acutely co-administered with ethinylestradiol, no direct interaction was found.

Elimination

Gestodene serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of 12 - 20 hours. Only metabolites of gestodene are excreted occurring at a urinary to biliary ratio of 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 about threefold when co-administered with ethinylestradiol. Following daily ingestion, gestodene serum levels increase about three to fourfold reaching steady-state conditions during the second half of a treatment cycle.

<u>Ethinylestradiol</u>

Absorption

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentration of about 30 - 80 pg/ml is reached within 1 - 2 hours.

Absolute bioavailability as a result of pre-systemic 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 - 18 L/kg was determined.

Metabolism

Ethinylestradiol is subject to pre-systemic 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 - 13 ml/min/kg.

Elimination

Ethinylestradiol serum levels decrease in two phases, the terminal disposition phase is characterised by a half-life of approximately 16 - 24 hours. Only metabolites of Ethinylestradiol are excreted occurring 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 - 4 days when serum ethinylestradiol levels are higher by 30 % to 40 % as compared to single dose.

5.3 Preclinical safety data

Toxicological studies have been performed on all components individually and on their combination.

Acute toxicity studies in animals showed no evidence of a risk of acute symptoms arising after accidental overdosage.

General safety studies with repeated administration have shown no evidence of any effects suggesting any unexpected risks in man.

Long-term and repeated dose carcinogenicity studies have not demonstrated any carcinogenic potential; however, it is important to remember that sex steroids are capable of promoting the development of certain tissues into hormone-dependent tumours.

Teratogenicity studies have not indicated any particular risk when oestrogen-progestogen combinations are used correctly; it is however essential to discontinue treatment immediately if taken in error at the beginning of pregnancy.

Mutagenicity studies have not revealed any mutagenic potential for ethinylestradiol or gestodene.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active yellow film-coated tablets

Tablet core:

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Polacrilin potassium

Tablet coat (*Opadry AMB yellow):*

Iron oxide yellow (E-172)

Lecithin (soya)

Polyvinyl alcohol

Talc

Titanium dioxide (E-171)

Xanthan gum.

Inactive white tablets (placebo)

Colloidal aluminium oxide

Lactose monohydrate

Magnesium stearate

Povidone K25

Silica, colloidal anhydrous

Sodium starch glycolate (type A).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C in a cool, dry place.

Store the blister pack in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

The tablets are contained in PVC-PVDC/aluminium blisters. Aluminium foil is a foil of push-through aluminium with a lacquered dull side, and a heat sealable bright side lacquered for sealing to PVC.

The blisters are contained in an outer cardboard carton.

Pack size: The 28-day pack (Every-day calendar pack) contains 24 active hormonal yellow film-coated tablets plus 4 inactive non-hormonal (placebo) white tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662 .

8. REGISTRATION NUMBER

47/18.8/0344

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 July 2022

10. DATE OF REVISION OF THE TEXT

TBA