1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

NORDETTE 150 ug/30 ug sugar-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each yellow active sugar-coated tablet of NORDETTE contains 150 µg of levonorgestrel and 30 ug of ethinyl estradiol.

Preservatives

Methyl parahydroxybenzoate 0,001 % *m/m*

Propyl parahydroxybenzoate 0,00076 % *m/m*

Contains sugar: Lactose monohydrate 32,97 mg, sucrose 22,456 mg

Each red inactive sugar-coated tablet of NORDETTE contains:

Preservative

Sodium benzoate 0,0018 % *m/m*

Contains sugar: Lactose monohydrate 38,006 mg, sucrose 25,686 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sugar-coated tablets

21 active yellow tablets: NORDETTE is a yellow, lustrous, round, biconvex sugar-coated

tablet.

7 red inert tablets: NORDETTE is a red, biconvex, sugar-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NORDETTE is indicated for:

- Fertility control in women.
- Control of cases of dysfunctional uterine bleeding.
- Symptomatic treatment of primary dysmenorrhoea where contraception is also desired.

4.2 Posology and method of administration

Posology

Adults

FOR CONTRACEPTION

To achieve maximum effectiveness, NORDETTE tablets must be taken as directed and at intervals not exceeding 24 hours. Patients should be instructed to take the tablets at the same time every day, preferably after the evening meal or at bedtime.

During the first cycle of administration, the patient is instructed to take one yellow tablet daily for 21 consecutive days, beginning on Day 1 of her menstrual cycle, i.e. the first day of bleeding.

One red inert tablet is taken daily for the next 7 consecutive days.

Withdrawal bleeding should usually occur 2 to 4 days after the last yellow tablet is taken.

During this first cycle, a mechanical, i.e. barrier, method of contraception should be supplemented until 14 tablets have been taken. If the tablets are begun after Day 5 or postpartum, it must be considered that ovulation and conception may have occurred before

the tablets were started.

The next and all subsequent courses will begin on the day after the last package was completed, even if withdrawal bleeding has not occurred or is still in progress. Each course of NORDETTE is thus begun on the same day of the week and follows the same schedule (21 days of yellow tablets, 7 days of red inert tablets) as the first course.

The patient who is changing from another oral contraceptive medicine will begin NORDETTE on the day she would usually start a new package of the other medicine. During the first NORDETTE cycle, a mechanical, i.e. barrier, method of contraception should be used until 14 consecutive tablets have been taken.

If transient spotting or breakthrough bleeding occurs, the patient is instructed to continue the regimen since such bleeding is usually without significance. If the bleeding is persistent or prolonged, the patient is advised to consult her healthcare provider.

If a patient is changing from 21-day combined oral contraceptives or from a combined Everyday pill (28-day tablets):

The first tablet of NORDETTE should be taken on the first day immediately after the end of the previous oral contraceptive course.

If a patient is changing from a progestogen-only pill (POP):

The first tablet of NORDETTE should be taken on the first day of bleeding, even if a POP has already been taken on that day. The remaining progestogen-only pills should be discarded.

Post-partum and post-abortum use

In the non-breastfeeding mother, NORDETTE may be begun immediately after delivery or at

the first postpartum examination, whether or not menstruation has resumed (see sections 4.3 and 4.6).

After pregnancy, oral contraception can be started 21 days after a vaginal delivery, provided that the patient is fully ambulant and there are no puerperal complications. Additional contraceptive precautions will be required for the first 7 days of tablet taking. Since the first port-partum ovulation may precede the first bleeding, another method of contraception should be used in the interval between childbirth and the first course of tablets (see sections 4.3 and 4.6).

After a first-trimester abortion, oral contraception may be started immediately.

Missed Tablets

The patient should be instructed to take a missed yellow tablet as soon as it is remembered. If two consecutive yellow tablets are missed, they should both be taken as soon as remembered. In either case, the next tablet should be taken at its usual time. Each time the patient misses one or two consecutive yellow tablets, a mechanical method of contraception should be supplemented until 14 consecutive daily tablets have been taken or until the package is finished if less than 14 yellow tablets remain.

If the patient misses one or more inert tablets, she is still protected against pregnancy, provided she begins the yellow tablets on the proper day. If three consecutive yellow tablets are missed, NORDETTE should be discontinued and the remainder of the package discarded. A new package should be started on the eighth day after the last tablet was taken. A mechanical method of contraception should be used until 14 consecutive daily tablets have been taken.

If withdrawal bleeding does not occur and NORDETTE has been taken according to

directions, it is unlikely that the patient has conceived. She should be instructed to begin a second course of NORDETTE on the usual day. If bleeding does not occur at the end of this second cycle, NORDETTE should not be taken until diagnostic procedures to exclude the possibility of pregnancy have been performed.
If the patient has not adhered to the prescribed regimen (missed one or more yellow tablets or started taking them on a day later than recommended), the probability of pregnancy should be considered at the time of the first missed period before NORDETTE is resumed.

Gastrointestinal upset:
Vomiting or diarrhoea may reduce the efficacy of NORDETTE by preventing full absorption. If vomiting or diarrhoea occurs within 4 hours of taking NORDETTE, tablet-taking from the current pack should be continued.

Additional non-hormonal methods of contraception (except the rhythm or temperature method) should be used during the gastrointestinal upset and for 7 days following the upset. If these 7 days overrun the end of a pack, the next pack should be started without a break.

In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be ruled out before starting the next pack. Other methods of contraception should be considered if the gastrointestinal disorder is likely to be prolonged.

FOR THE SYMPTOMATIC TREATMENT OF PRIMARY DYSMENORRHOEA AND CASES OF DYSFUNCTIONAL UTERINE BLEEDING - Dosage as for contraception.

Special populations

Elderly populations

Not applicable.

Paediatric population

Not applicable.

Method of administration

For oral administration.

4.3 Contraindications

NORDETTE is contraindicated in:

- Patients with hypersensitivity to ethinylestradiol or levonorgestrel or to any of the excipients in NORDETTE (see section 6.1).
- Concomitant use with medicines containing ritonavir (see section 4.4 and 4.5).
- Patients with depression not well controlled with treatment.
- Patients with a history of depression with the use of hormonal contraceptives.
- Patients with recurrent cholestatic jaundice, or impaired liver function.
- Patients with known or suspected estrogen-dependent neoplasia.
- Patients with thrombophlebitis or thromboembolic disorders, or a history thereof (e.g. previous proven deep-vein thrombosis (DVT), previous pulmonary embolism and inherited thrombophilia).
- Patients with cerebrovascular insufficiency.
- Patients with coronary-artery disease.
- Undiagnosed vaginal bleeding.
- Patients where migraine becomes focal or when there is a loss of vision, or if there is an onset of unexplained chest pain (severe migraine). NORDETTE should be discontinued

immediately upon onset of these symptoms.

- Patients with known or suspected carcinoma of the breast.
- Patients with personal and family history of breast cancer.
- The presence or history benign or malignant liver tumours which developed during the use of oral contraceptives or estrogen-containing medicines.
- The presence (active liver disease) or history of severe hepatic disease, e.g. active viral hepatitis and severe cirrhosis, as long as liver function values have not returned to normal.
- The presence or risk of venous thromboembolism (VTE)
  - Venous thromboembolism - current VTE (on anticoagulants) or history of e.g. deep venous thrombosis (DVT) or pulmonary embolism (PE).
  - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance (including Factor V Leiden), antithrombin - III - deficiency, protein C deficiency, protein S deficiency.
  - Major surgery with prolonged immobilisation (see section 4.4).
  - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4).
- The presence or risk of arterial thromboembolism (ATE)
  - Arterial thromboembolism - current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris).
  - Cerebrovascular disease - current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack (TIA)).
- Patients with known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin-antibodies, lupus anticoagulant).

- Patients with a history of migraine with focal neurological symptoms.
- Patients known with inherited genetic mutations: BRCA1 and BRCA 2 genes.
- Early menstrual periods (before the age of 12 years).
- History of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma *in situ*.
- Previous treatment using radiation therapy to the chest or breast.
- Previous exposure to diethylstilbestrol (DES).

- A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms,
    - severe hypertension,
    - severe dyslipoproteinaemia.
- Relative contraindications include
    - a history of diabetes mellitus,
    - epilepsy,
    - asthma,
    - hypertension,
    - depression,
    - porphyria,
    - Dubin Johnson's syndrome,
    - Rotor syndrome,
    - or states in which fluid retention occur.
- Concomitant use with medicines containing ombitasvir/paritaprevir/ritonavir, dasabuvir, glecaprevir/pibrentasvir and ofosbuvir/velpatasvir/voxilaprevir (see sections 4.4 and 4.5).

- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

CIGARETTE SMOKING

CIGARETTE SMOKING INCREASES THE RISK OF SERIOUS CARDIOVASCULAR SIDE EFFECTS FROM THE USE OF NORDETTE. THE RISK INCREASES WITH AGE AND WITH HEAVY SMOKING (15 OR MORE CIGARETTES PER DAY) AND IS MARKED IN WOMEN OVER 35 YEARS OF AGE. WOMEN WHO USE ORAL CONTRACEPTIVES SUCH AS NORDETTE SHOULD BE STRONGLY ADVISED NOT TO SMOKE.

UNDER NO CIRCUMSTANCES SHOULD THE ORAL CONTRACEPTIVE TABLET BE STOPPED WITHOUT HAVING ADOPTED A SATISFACTORY ALTERNATIVE METHOD OF CONTRACEPTION.

Missed tablets - See section 4.2.

If any of the conditions or risk factors mentioned below are present, the suitability of NORDETTE should be discussed with the woman. In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of NORDETTE should be discontinued.

Ocular lesions

Discontinue NORDETTE and institute appropriate diagnostic and therapeutic measures if there is a gradual or sudden, partial or complete loss of vision, proptosis or diplopia, papilloedema, or any evidence of retinal vascular lesions or optic neuritis.

Carcinoma

Ovarian, endometrial, cervical and breast cancer have been reported in women using combined oral contraceptives such as NORDETTE. Data suggests that long-term continuous

administration of either natural or synthetic estrogen increases the frequency of carcinoma of the breast, cervix, vagina and liver. Under the influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

Close clinical surveillance is essential in all women taking these preparations.

Breast cancer

NORDETTE contains estrogen and progestogen which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a significant increase in the risk of developing breast cancer in 55 575 women 40 to 59 years of age who used menopausal hormone therapy (MHT). The risk increased steadily with duration of use and was slightly greater for estrogen-progestogen than estrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for estrogen-progestogen preparations was 1,60 at 1 to 4 years and RR = 2,08 at 5 to 14 years, while that for estrogen only preparations was 1,17 at 1 to 4 years and 1,33 at 5 to 14 years. There was no risk of to develop breast cancer in women who started MHT at 60 years of age.
All women on NORDETTE should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. Mammography evaluations should be done based on patient age, risk factors, and prior mammogram results.

Cervical cancer

The most important risk factor for cervical cancer is persistent HPV infection. Long-term use of COCs, such as NORDETTE, may further contribute to this increased risk.

Liver cancer

Benign hepatic adenomas have been associated with the use of oral contraceptives such as

NORDETTE. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage.

This has been reported in short- and long-term users of oral contraceptives. Such lesions may present as an abdominal mass or with signs and symptoms of an acute abdomen and should be considered if the patient has abdominal pain and tenderness, liver enlargement or evidence of intra-abdominal bleeding. NORDETTE should be discontinued if persistent upper abdominal pain develops and the possibility of a liver tumour should be included in the differential diagnosis.

Headache

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

Use during or immediately preceding pregnancy

Serum folate levels may be depressed by oral contraceptives' use. Women who become pregnant shortly after discontinuing these medicines may have a greater chance of developing folate deficiency and its complications.

Foetal abnormalities, including heart defects and limb defects, have been reported in offspring of women who have taken oral contraceptives in early pregnancy. Pregnancy should be ruled out before NORDETTE is begun and considered in women who have missed two consecutive menstrual periods. The possibility of pregnancy should be considered at the first missed menstrual period in a patient who has not adhered to the prescribed regimen.

Further oral contraceptive use should be withheld until pregnancy has been ruled out. In

women who discontinue oral contraceptives with the intent of becoming pregnant, a nonhormonal method of contraception is recommended for 3 months before attempting to conceive.

Female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestins are effective for these uses.

The administration of progestin-only or estrogen-progestin combinations to induce withdrawal bleeding should not be used as a test for pregnancy.

Conditions which deteriorate in pregnancy or during previous COC use

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use. Consideration should be given to stopping NORDETTE if any of the following occur during use:

- Cholestatic jaundice has been reported in users of NORDETTE. If this occurs, this medicine should be discontinued. Patients with a history of jaundice during pregnancy should be carefully observed during NORDETTE therapy.
- Pruritus related to cholestasis.
- NORDETTE may increase the risk of gallstone formation and may worsen existing disease.
- Systemic lupus erythematosus.
- Herpes gestationis.
- Otosclerosis-related hearing loss.
- Sickle cell anaemia.
- Renal dysfunction.

- Hereditary angioedema.
- Porphyria.
- Cervical cancer.
- Any other condition an individual woman has experienced worsening of during pregnancy or previous use of COCs.

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Ectopic pregnancy

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

Bleeding irregularities

Breakthrough bleeding, spotting and amenorrhoea are frequent reasons for patients discontinuing NORDETTE. The incidence is in the order of 1 % of users.

In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, non-functional causes should be borne in mind. In undiagnosed persistent or recurrent bleeding from the vagina, appropriate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem.

Changing to a regimen with a higher estrogen content, while potentially useful in minimising menstrual irregularity, should be done only if necessary, since this may increase the risk of thromboembolic disease.

Women with a history of oligomenorrhoea or secondary amenorrhoea or young women

without regular cycles may have a tendency to remain anovulatory or to become amenorrhoeic after discontinuation of NORDETTE. Women with these pre-existing problems should be advised of this possibility and encouraged to use another method of contraception. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

Menstrual changes

- *Reduction of menstrual flow:* This is not abnormal, and it is to be expected.
- *Missed menstruation:* Occasionally, withdrawal bleeding may not occur at all. If the tablets have been taken correctly, pregnancy is unlikely. If withdrawal bleeding fails to occur at the end of a second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.
- *Intermenstrual bleeding:* 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. This may include curettage.

Thromboembolic disorders

- *Risk of venous thromboembolism (VTE):*

The use of any combined oral contraceptive (COC) such as NORDETTE increases the risk of venous thromboembolism (VTE).

The decision to use NORDETTE should be taken after a discussion with the woman to ensure she understands the risk of VTE with NORDETTE how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4

weeks or more.

Thrombosis has also been reported to occur in COC users in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries.

- *Risk factors for VTE:*

The risk for venous thromboembolic complications in COC users may increase substantially in a woman with additional risk factors; particularly if there are multiple risk factors (see Table 1). NORDETTE is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a COC should not be prescribed (see section 4.3).

Table 1: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors are also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation including air travel > 4 hours can also be a risk factor for VTE, particularly in women with other risk factors.	In these situations, it is advisable to discontinue use of NORDETTE (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if NORDETTE has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50 years).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.
Other medical conditions associated with VTE.	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
Increasing age	Particularly above 35 years.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

- *Symptoms of VTE (deep vein thrombosis and pulmonary embolism):*

In the event of symptoms, women should be advised to seek urgent medical attention and to inform the healthcare provider that she is taking NORDETTE.

Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot or along a vein in the leg,
- 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.

Symptoms of pulmonary embolism (PE) can include:

- sudden onset of unexplained shortness of breath or rapid breathing,
- sudden coughing which may be associated with haemoptysis,
- sharp chest pain,
- severe light-headedness or dizziness,
- rapid or irregular heartbeat.

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).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discolouration of an extremity. If the occlusion occurs in the eye, symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

- **Risk of arterial thromboembolism (ATE):**

Epidemiological studies have associated the use of COCs such as NORDETTE, is associated with an increased risk for arterial thromboembolism (myocardial infarction) or for

cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

- *Risk factors for ATE:*

The risk of arterial thromboembolic complications or of a cerebrovascular accident in COC users increases in women with risk factors (see Table 2). NORDETTE is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3).

If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative, NORDETTE should not be prescribed (see section 4.3).

Table 2: Risk factors for ATE

Risk factor	**Comment**
Increasing age.	Particularly above 35 years.
Smoking	Women should be advised not to smoke if they wish to use NORDETTE. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension.	
Obesity (body mass index (BMI) over 30 kg/m^2).	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors.
Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50 years).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any NORDETTE use.
Migraine.	An increase in frequency or severity of migraine during NORDETTE use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.

Other medical conditions associated with adverse vascular events.	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

- *Symptoms of ATE:*

In the event of symptoms, women should be advised to seek urgent medical attention and to inform the healthcare provider that she is taking NORDETTE.

Symptoms of a cerebrovascular accident can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body,
- sudden trouble walking, dizziness, loss of balance or coordination,
- sudden confusion, trouble speaking or understanding,
- sudden trouble seeing in one or both eyes,
- sudden, severe or prolonged headache with no known cause,
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (MI) can include:

- 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,
- feeling of being full, having indigestion or choking,
- sweating, nausea, vomiting or dizziness,
- extreme weakness, anxiety, or shortness of breath,
- rapid or irregular heartbeats.

Other conditions

Certain chronic diseases may deteriorate during the use of combined oral contraceptives

such as NORDETTE.

Myocardial infarction and coronary artery disease

An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported. Studies found that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolaemia, obesity, diabetes, history of pre-eclampsia), the higher the risk of developing myocardial infarction. Oral contraceptives were found to be a clear additional risk factor.

Carbohydrate and lipid metabolic effects

A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives such as NORDETTE. For this reason, prediabetic and diabetic patients should be carefully observed while receiving NORDETTE. An increase in triglycerides and total phospholipids has been observed in patients receiving NORDETTE.

Diabetes (without vascular involvement)

Insulin-dependent diabetics without vascular disease can use NORDETTE. However, it should be remembered that all diabetics are at an increased risk of arterial disease and this should be considered when prescribing NORDETTE. Diabetics with existing vascular disease are contraindicated from using NORDETTE (see section 4.3). Although NORDETTE 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, such as NORDETTE (containing < 0,05 mg ethinyloestradiol). However, diabetic women should be carefully observed while taking NORDETTE.

Known hyperlipidaemias

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of

pancreatitis when using COCs such as NORDETTE. Women with hyperlipidaemias are at an increased risk of arterial disease (see Risk of arterial thromboembolism (ATE)).

Blood pressure

Hypertension is a risk factor for stroke and myocardial infarction (see Risk of arterial thromboembolism (ATE)). In some women, hypertension may occur within a few months of beginning use. In the first year of use, the prevalence of women with hypertension is low but the incidence increases with increasing exposure. Age is also strongly correlated with the development of hypertension in oral contraceptive users.

Women who previously have had hypertension during pregnancy may be more likely to develop an elevation of blood pressure when given NORDETTE. If hypertension develops during the use of NORDETTE, antihypertensive treatment should normally be initiated at a blood pressure level of 160/100 mm Hg in uncomplicated patients or at 140/90 mm Hg in those with target organ damage, established cardiovascular disease, diabetes or with increased cardiovascular risk factors.

Decisions about the continued use of NORDETTE should be made at lower BP levels, and alternative contraception may be advised. Hypertension that develops as a result of taking NORDETTE usually returns to normal after discontinuing NORDETTE.

Disturbances of liver function

Acute or chronic disturbances of liver function may necessitate the discontinuation of NORDETTE use until markers of liver function return to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs, such as NORDETTE.

Psychiatric disorders

Mood changes and depression are side effects reported with the use of hormonal contraceptives including NORDETTE. There is some evidence that hormonal contraceptive use may be associated with severe depression and a higher risk of suicidal thoughts/behavior (e.g. talking about suicide, withdrawing from social contact, having mood swings, being pre-occupied with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs, doing self-destructive things, personality changes) and suicide. Prescribers should inform their patients to contact their doctor for advice if they experience mood changes and depression whilst on treatment with NORDETTE.

Chloasma

Chloasma may occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking NORDETTE.

Gallbladder Disease

An increased risk of surgically confirmed gallbladder disease in users of estrogens and oral contraceptives have been reported.

Reduced efficacy

The efficacy of NORDETTE may be reduced, in the event of missed tablets, vomiting or diarrhoea, or concomitant medication (see section 4.2).

ALT elevations

Patients treated for hepatitis C virus infections (HCV) with the medicines containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more

frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs) . ALT elevations have also been observed with HCV anti-viral medicines containing glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.3 and 4.5).

Medical examination/consultation

Prior to the initiation or reinstitution of NORDETTE, a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured, and a physical examination should be performed, guided by the contraindications (see sections 4.3 and 4.4).

It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of NORDETTE compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

The woman should also be instructed to carefully read the Patient Information Leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

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

Undiagnosed vaginal bleeding that is suspicious for underlying conditions should be investigated.

Laboratory tests and investigations should include but not be limited to Papanicolaou smears, blood glucose levels, liver- and kidney function tests, and monitoring of existing conditions. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and breast, abdominal and pelvic examination including cervical cytology.

Patient education should include: recognition of VTE and ATE symptoms and associated risk

factors, protection against contracting HIV and sexually transmitted diseases, informing a healthcare provider of NORDETTE use prior a major surgery and reporting of worsening of existing medical conditions or side effects.

Conditions which require strict medical supervision

The decision to prescribe the COC must be made using clinical judgement and in consultation with the woman.

Exacerbation or first appearance of any of these conditions or risk factors may indicate that use of the oral contraceptive should be discontinued.

The woman should contact her healthare provider, who should then decide on whether COC use should be discontinued:

- Diabetes mellitus with mild vascular disease or mild nephropathy, retinopathy or neuropathy.
- Hypertension that is adequately controlled, i.e. systolic > 140 to159 mm Hg or diastolic > 90 to 94 mm Hg (see also Section 4.4 'Reasons for stopping oral contraception immediately').
- Porphyria.
- Obesity.
- Migraine.
- Cardiovascular diseases.

Reasons for stopping oral contraception immediately:

When stopping oral contraception, non-hormonal contraception should be used to ensure contraceptive protection is maintained.

1. Occurrence for the first time, or exacerbation, of migrainous headaches or unusually

frequent or unusually severe headaches.

2. Sudden disturbances of vision, of hearing or other perceptual disorders.

3. First signs of thrombosis or blood clots (e.g. unusual pains in or swelling of the leg(s), stabbing pains on breathing or coughing for no apparent reason). Feeling of pain and tightness in the chest.

4. Six weeks before an elective major operation (e.g. abdominal, orthopaedic), any surgery to the legs, medical treatment for varicose veins or prolonged immobilisation, e.g. after accidents or surgery. Do not restart until 2 weeks after full ambulation. In case of emergency surgery, thrombotic prophylaxis is usually indicated e.g. subcutaneous heparin.

5. Onset of jaundice, hepatitis, itching of the whole body.

6. Significant rise in blood pressure.

7. Severe upper abdominal pain or liver enlargement.

8. Clear exacerbation of conditions known to be capable of deteriorating during oral contraception or pregnancy (see section 4.4 'Conditions which deteriorate in pregnancy or during previous COC use' under 'Other conditions').

Porphyria:

Safety has not been established.

Excipients

Lactose and sucrose warning:

NORDETTE contains lactose monohydrate and sucrose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, or fructose intolerance the Lapp lactase deficiency, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Enzyme inducers

Medicines which induce hepatic enzymes (especially cytochrome P450 3A4) can increase the clearance and increase the metabolism of NORDETTE and hence **may result in breakthrough bleeding and/or contraceptive failure (i.e. pregnancy).**

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of NORDETTE enzyme induction may be sustained for about 4 weeks.

Women on short term treatment with any of these medicines should temporarily use a barrier method in addition to the COC, such as NORDETTE, or choose another method of contraception. The barrier method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation.

If the period during which the barrier methods used runs beyond the last active (yellow) tablet, the user should finish taking all the active tablets, discard the inert (red) tablets and start a new pack of NORDETTE the next day with an appropriate active (yellow) tablet. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed during the tablet free interval following the end of the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be used.

The following have been shown to have clinically important interactions with NORDETTE:

Antiretroviral medicines

- Ritonavir,
- nelfinavir,

- nevirapine.

There are other antiretroviral medicines that may increase plasma concentration of sex hormones.

Anticonvulsants

- barbiturates (including phenobarbitone),
- primidone,
- phenytoin,
- carbamazepine,
- oxcarbazepine,
- topiramate**,**
- felbamate.

Antibiotics/antifungals

Women on short-term treatment with these antibiotics must temporarily use a barrier contraceptive method concomitantly with the contraceptive tablets. Oral contraceptive failure may occur with concomitant antibiotic therapy. For maximal protection, additional non-hormonal contraception is recommended for the duration of antibiotic therapy and for seven days thereafter. Those on long-term antibiotic therapy need only take extra precautions for the first two weeks of antibiotic therapy. Spotting and breakthrough bleeding are possible signs of diminished contraceptive effectiveness.

- griseofulvin,
- ampicillin,
- penicillin v,
- tetracycline,
- rifampicin,
- neomycin,
- chloramphenicol,

- sulphonamides,
- nitrofurantoin.

Herbal remedies

- St. John's wort (*Hypericum perforatum*).

Substances decreasing the clearance of COCs (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), and macrolides (e.g. erythromycin) can increase plasma concentrations of the estrogen or the progestin or both.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1,4 to 1,6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0,035 mg ethinylestradiol.

Substances with variable effects on the clearance of COCs, e.g.: When co-administered with NORDETTE

Many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.

Effects on other medicines

NORDETTE may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin, theophylline) or decrease (e.g. lamotrigine).

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

Pharmacodynamic interactions

Concomitant use with medicines containing ombitasvir/paritaprevir/ritonavir, dasabuvir, with or without ribavirin, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir, may increase the risk of ALT elevations (see sections 4.3 and 4.4).

Therefore, NORDETTE users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination medicine regimen. NORDETTE can be restarted 2 weeks following completion of treatment with this combination medicine regimen.

Laboratory tests

The use of NORDETTE 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. Laboratory staff should therefore be informed about NORDETTE use when laboratory tests are requested.

- Increased prothrombin and Factors VII, VIII, IX and X; decreased antithrombin-III; increased noradrenaline-induced platelet aggregation.
- Increased thyroid-binding globulin (ITBG) leading to increased circulating total-thyroid hormone, as measured by protein bound iodine (PBI), T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
- Decreased pregnanediol excretion.
- Reduced response to metyrapone test.
- Increased sulphobromophthalein retention.

The results of these tests should not be regarded as reliable until NORDETTE use has been discontinued for 1 to 2 months. Abnormal tests should then be repeated. NORDETTE may produce false positive results when neutrophil alkaline phosphatase activity is evaluated for the early diagnosis of pregnancy.

A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, diabetic patients should be carefully observed while on NORDETTE therapy.

4.6 Fertility, pregnancy and lactation

The use of NORDETTE is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

If pregnancy occurs during treatment with NORDETTE, further intake must be stopped immediately.

Foetal abnormalities including heart defects and limb defects, have been reported in offspring of women who have taken oral contraceptive in early pregnancy (see section 4.4).

Lactation

Mothers taking NORDETTE should not breastfeed their infants (see section 4.3). The use of NORDETTE during lactation may lead to a reduction in the volume of milk produced and to a change in its composition. The active substances are excreted with the milk. These amounts may affect the child particularly in the first 6 weeks postpartum. Mothers who are breastfeeding their infants are advised to use another method of contraception.

Fertility

There is no fertility data.

4.7 Effects on ability to drive and use machines

NORDETTE has none or negligible influence on the ability to drive and use machines. Since adverse reactions such as dizziness have been reported in patients receiving NORDETTE patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that NORDETTE does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

The most commonly reported adverse reactions with NORDETTE are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. They occur in ≥ 1 % of users.

Serious adverse reactions are arterial and venous thromboembolism.

The following adverse events have been reported during use of ethinylestradiol / levonorgestrel:

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations	Vaginitis, including candidiasis		
Neoplasm benign, malignant and unspecified (including cysts and polyps)		Liver tumours (benign and malignant), breast cancer, cervical cancer	
Immune system disorders		Hypersensitivity, exacerbation of hereditary angioedema[#]	

Metabolism and nutrition disorders		Hypertrigliceridaemia, increase or decrease in mass, changes in appetite	Precipitation of acute attack of porphyria
Psychiatric disorders	Depressive moods, altered mood, nervousness	Decreased libido, increased libido.	Severe depression with a higher risk of suicidal thoughts/behavior and suicide[#]
Nervous system disorders	Headache	Migraine, dizziness	Exacerbation of chorea[#]
Eye disorders		Changes in corneal curvature (steepening), intolerance to contact lenses, cataracts	
Cardiac disorders		An increased risk of myocardial infarction	
Vascular disorders		Hypertension, venous thromboembolism (VTE), arterial thromboembolism (ATE). An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke (e.g. ischaemic stroke, haemorrhagic stroke), transient ischaemic attacks, venous thrombosis and pulmonary embolism	
Gastrointestinal disorders	Nausea, abdominal pain	Diarrhoea, vomiting, abdominal cramps, bloating, gastrointestinal irritation and pancreatitis	Crohn's disease, ulcerative colitis[#]
Hepato-biliary disorders		Liver function disturbances[#], gallbladder disease, cholestatic jaundice, exacerbation of existing disease	
Skin and subcutaneous tissue disorders	Acne	Rash, urticarial erythema nodosum, erythema multiforme, melasma which may be persistent, skin pigmentation	Hirsutism, loss of scalp hair, haemorrhagic eruption, chloasma [#,]
Musculoskeletal and connective tissue disorders		Systemic lupus erythematosus	

Renal and urinary disorders			Cystitis like syndrome, haemolytic uremic syndrome
Reproductive system and breast disorders	Breast pain, breast tenderness, spotting, breakthrough bleeding	Vaginal discharge, ,change in cervical erosion or cervical secretion, premenstrual-like syndrome, breast hypertrophy, breast secretion	Reduced menstrual flow[#], spotting[#] and missed withdrawal bleeding[#], post pill amenorrhoea[#]
General disorders and administrative site conditions		Fluid retention/oedema	
Investigations	Increased weight	Increase in blood pressure, decrease weight, changes in serum lipid levels	

[#] adverse events reported post marketed.

c) Description of selected adverse reactions

An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs (see section 4.4) .

The following serious adverse events have been reported in women using COCs, which are discussed in section 4.4 'Special warnings and precautions for use':

• Venous thromboembolic disorders.

• Arterial thromboembolic disorders.

• Strokes (e.g. transient ischemic attack, ischemic stroke, haemorrhagic stroke).

• Hypertension.

• Liver tumours (benign and malignant).

• Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation

to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see sections 4.3 and 4.4.

Conditions reported to deteriorate with pregnancy or previous COC use:
Jaundice and/or pruritus related to cholestasis; gallstone formation; systemic lupus erythematosus; herpes gestationis; otosclerosis-related hearing loss; sickle cell anaemia; renal dysfunction; hereditary angioedema; porphyria; cervical cancer.
Changes in glucose tolerance or effect on peripheral insulin resistance have been reported in women using COCs (see section 4.4).

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 providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/Publications/Index/8.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/+2711 239 6200

4.9 Overdose

Symptoms

Overdosage may cause nausea, vomiting and withdrawal bleeding may occur in females. Withdrawal bleeding may even occur in girls before their menarche, if they accidentally take NORDETTE.

Treatment

Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 18.8 Ovulation controlling agents.

Pharmacotherapeutic group: Hormonal contraceptives for systemic use, progestogens and estrogens, fixed combinations

ATC code: G03AA07

Mechanism of action

Oral contraceptives of the combination type act by a multiplicity of mechanisms. Ovulation is inhibited by suppression of gonadotropin release, particularly the mid-cycle peaks and the viscosity of the cervical mucous is increased, impairing sperm penetration, and an endometrium less receptive for implantation is formed.

5.2 Pharmacokinetic properties

Absorption

Ethinyl estradiol and levonorgestrel are well absorbed from the gastrointestinal tract. Ethinyl estradiol is subject to considerable first-pass metabolism with a mean bioavailability of 40 to 45 %. Levonorgestrel does not undergo first-pass metabolism and is therefore completely bioavailable.

Distribution

Levonorgestrel is extensively plasma protein bound both to sex hormone binding globulin (SHBG) and albumin. Ethinyl estradiol, however, is bound in plasma only to albumin and enhances the binding capacity of SHBG. Following oral administration, peak plasma levels of each medicine occur within 1 to 4 hours.

Biotransformation

Ethinyl estradiol is primarily metabolised by aromatic hydroxylation but a wide variety of

hydroxylated and methylated metabolites are formed, and these are present both free and as conjugates with glucuronide and sulphate.

Levonorgestrel is primarily metabolised by reduction of the A ring followed by glucuronidation.

Elimination

The elimination half-life for ethinyl estradiol is approximately 25 hours. Conjugated ethinyl estradiol is excreted in bile and subject to enterohepatic recirculation. About 40 % of ethinyl estradiol is excreted in the urine and 60 % is eliminated in the faeces. The elimination half-life for levonorgestrel is approximately 24 hours. About 60 % of levonorgestrel is excreted in the urine and 40 % is eliminated in the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active tablets

Calcium carbonate, iron oxide yellow (C.I. 77492), lactose monohydrate, magnesium stearate, maize starch, methyl parahydroxybenzoate, polyethylene glycol, Povidone, Povidone 25, Povidone 90F, propyl parahydroxybenzoate, purified talc, sucrose refined white H1, titanium dioxide (C.I. 77891), waradur XE.

Each red inactive sugar-coated tablet contains

Calcium carbonate, colour FD&C Red No.3 aluminium lake (C.I. 45430), FD&C yellow # 6/sunset yellow FCF (C.I. 15985), magnesium stearate, microcrystalline cellulose PH 102, polyethylene glycol, Ponceau 4R aluminium lake (C.I. 16255), povidone, quinoline yellow aluminium lake (C.I. 47005), purified talc, Povidone 90F, sodium benzoate, sucrose refined white H1, Tablettose 80, waradur XE.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

28 tablets consisting of 21 yellow active tablets and 7 red inert tablets. The tablets are packed in clear polyvinyl chloride blister strips sealed with an aluminium foil backing. One blister strip is packed into a pre-printed cardboard carton together with a leaflet.
28 tablets consisting of 21 yellow active tablets and 7 red inert tablets. The tablets are packed in clear polyvinyl chloride blister strips sealed with an aluminium foil backing. 100 strips together with 100 leaflets are packed into a shipper carton.
Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

F/18.8/229

9. DATE OF FIRST AUTHORISATION

25 November 1974

10. DATE OF REVISION OF TEXT

03 June 2023

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