1. NAAM VAN HET GENEESMIDDEL

Kosidina 0,075 mg/0,030 mg 21+7, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each white tablet contains 0.075 mg (equivalent to 75 micrograms) gestodene and 0.030 mg (equivalent to 30 micrograms) ethinylestradiol

Each placebo green tablet does not contain active substances.

Excipient(s) with known effect

Each active white tablet contains 59.12 mg lactose monohydrate.

Each placebo green tablet contains 55.5 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Active tablet: Round, white tablets, with a diameter of 5.7 mm approximately. The tablet is debossed with a '*C'* on one side and '*33'* on the other side.

Placebo tablets: Round, green film-coated tablets, with a diameter of 5 mm approximately.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

The decision to prescribe [nationally completed name] should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with [nationally completed name] compares with other CHCs (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Posology

How to take [nationally completed name]
The tablets must be taken every day at approximately the same time, if necessary with a little liquid, in the order indicated on the blister pack. One white active tablet per day should be taken for 21 days and then a green placebo tablet for the last 7 days. You must then start a new pack straightaway (21 white

and then 7 green tablets). There is therefore no gap between packs. A withdrawal bleeding will occur usually on the 2nd or 3rd day taking the placebo green tablets, and may not stop until the next pack is started.

How to start taking [nationally completed name]
If no preceding hormonal contraceptive use in the past month
Taking of the tablets should begin on the first day of the woman's natural cycle (i.e. on the first day of the woman's menstrual bleeding). One may begin taking the pills on day 2-5, but in these cases, it is recommended that a barrier method also be used for the first 7 days on which pills are taken during the first cycle.

Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch
The woman should start taking [nationally completed name] on the next day after taking the last active tablet in her previous package of contraceptive pills – but no later than the day after the usual tablet-free or placebo-tablet period of her previous contraceptive pill. In case a vaginal ring or transdermal patch has been used, the woman should start using [nationally completed name] preferably on the day of removal, but at the latest when the next application would have been due.

When changing from progestogen-only preparations (progestogen-only pills, injection, implant, or from a progestogen-releasing intrauterine system (IUS)):
The woman may change from progestogen-only pills (POPs) on any day. The first tablet should be taken on the day after any tablet of the POP package. When changing from an implant or the IUS, [nationally completed name] should be started on the day the implant is removed. When changing from injections, [nationally completed name] should be started when the next injection is due to be given. In all
these cases, the woman is advised to also use a barrier method for the first 7 days of taking the pills.

After an abortion in the first trimester
The woman may start taking the pills immediately. If she does so, no further contraceptive steps need be taken.

After delivery or abortion in the second trimester
For breastfeeding women - see section 4.6.
The woman should be advised to begin taking the tablets on day 21- 28 after delivery in non- lactating women or after abortion in the second trimester. If she starts later, she should be advised to also use a barrier method during the first 7 days of taking the pills. If she has already had intercourse, the possibility of pregnancy should be excluded before she begins taking the pills, or she should wait for her first menstruation.

Management of missed tablets
Missing a tablet for less than 12 hours does not diminish the contraceptive protection. The woman should take the tablet as soon as she remembers, and continue taking the rest of the tablets as usual.

Missing a tablet for more than 12 hours can diminish the contraceptive protection. The two following rules may be helpful in dealing with missed tablets.
1. Taking of the tablets should never be discontinued for longer than 7 days.

2. It takes 7 days of uninterrupted ingestion of the tablets to achieve sufficient suppression of the hypothalamus-pituitary-ovarian axis. Thus, the following advice can be given in daily practice:

Week 1
The user should take the last missed tablet as soon as she remembers, even if this means that she needs to take 2 tablets at the same time. From then on, she should continue to take the tablets at the usual time. At the same time, she should use a barrier method, i.e. a condom, for the next 7 days. If she had intercourse during the past 7 days, she should consider the possibility that she might be pregnant. The more tablets have been missed, and the closer this happened to the monthly tablet- free period, the higher the risk of pregnancy.

Week 2
The user should take the last missed tablet as soon as she remembers, even if this means that she needs to take 2 tablets at the same time. From then on, she should continue to take the tablets at the usual time. If the tablets have been taken correctly for the 7 days prior to the missed tablet, it is not necessary to take any additional contraceptive precautions. If this is not the case, however, or if more than 1 tablet has been missed, the woman should use a barrier method**,** i.e. a condom for the next 7 days.

Week 3
The risk of reduced protection is imminent because of the approaching of the placebo days. The reduced contraceptive protection can be prevented, however, by adjusting the intake of the tablets. By adhering to either of the following two options, it is, therefore, not necessary to take any additional contraceptive precautions, provided that the tablets have been taken correctly for the 7 days prior to the missed tablet. If this is not the case, the woman should be advised to follow the first of the two choices, and at the same time use a barrier method**,** i.e. a condom for the next 7 days.

1. The user should take the last missed tablet as soon as she remembers even if this means that she needs to take 2 tablets at the same time. From then on, she should continue to take the tablets at the usual time. She begins the next pack immediately after she took the last tablet from the current package; that means no pause between packages. The user will probably not get her menstruation before the end of the second package, but she may experience spotting or withdrawal bleeding on the days when she takes the tablets.

2. The woman can also be advised to stop taking tablets from the current package. In that case, she should have a period taken placebo tablets for up to 7 days, including the days when she missed the tablets, and subsequently continue with the next pack.

If the woman missed the tablets, and subsequently did not get her menstruation in the first normal placebo period, she should consider the possibility that she may be pregnant.

Advice in case of gastro-intestinal disturbances
In case of severe gastro-intestinal disturbances (e.g., vomiting or diarrohoea), absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3- 4 hours after tablet-taking, a new (replacement) tablet should be taken as soon as possible. The new tablet should be taken within 12 hours of the usual time of tablet-taking if possible. If more than 12 hours elapse, the advice concerning missed tablets, as given in section 4.2 “Management of missed tablets”,

is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another blister pack.

How to postpone a withdrawal bleed
To delay a period the woman should continue with another blister pack of [nationally completed name] without taking the green placebo tablets. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of [nationally completed name] is then resumed after the usual 7-day taking placebo tablets.
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 internal taking placebo tablets by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

Children and adolescents
[nationally completed name] is only indicated after menarche.

Method of administration
Oral use

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following conditions. Should any of the conditions appear for the first time during CHC use, the product should be stopped immediately.

- 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)

- 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)

  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
  - History of migraine with focal neurological symptoms.

- A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
  - diabetes mellitus with vascular symptoms
  - severe hypertension
  - severe dyslipoproteinaemia

- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breast)
- Presence or history of severe hepatic disorders, as long as liver function tests are not normalised
- Presence or history of benign or malignant liver tumours
- Undiagnosed vaginal bleeding
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

[nationally completed name] is contraindicated for concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, medicinal products containing glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

4.4 Special warnings and precautions for use

Warnings

If any of the conditions or risk factors mentioned below is present, the suitability of [nationally completed name] 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 [nationally completed name] should be discontinued.

In case of suspected or confirmed VTE or ATE, CHC use should be discontinued. In case anti-coagulant therapy is started, adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

Risk of venous thromboembolism (VTE)

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as [nationally completed name] may have up to twice this level of risk. The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with [nationally completed name], 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.

In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

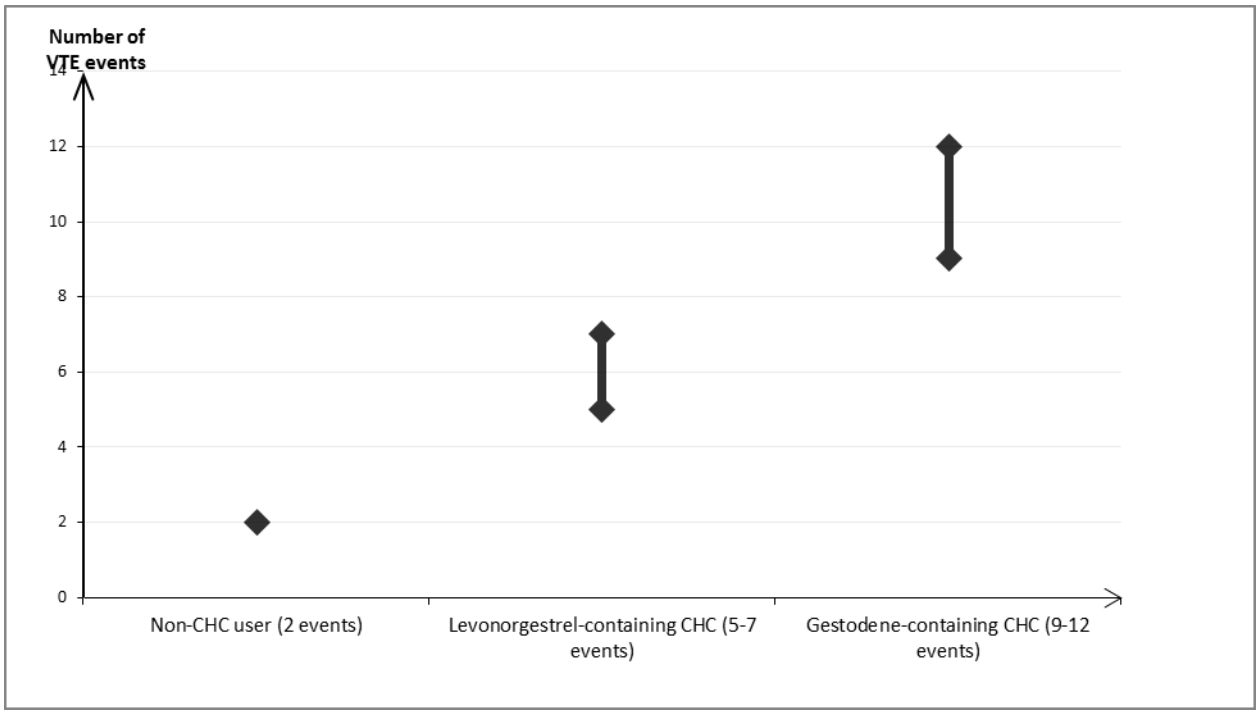
It is estimated[1] that out of 10,000 women who use a CHC containing gestodene between 9 and 12 women will develop a VTE in one year; this compares with about 6[2] in women who use a levonorgestrel-containing CHC.

In both cases, the number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period.

1 These incidences were estimated from the totality of the epidemiological study data, using relative risks for the different products compared with levonorgestrel-containing CHCs.
2 Mid-point of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6

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

Number of VTE events per 10,000 women in one year



Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

Risk factors for VTE

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table). [nationally completed name] 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 CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index over 30 kg/m²)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors 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 the patch/pill/ring (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 [nationally completed name] 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).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC 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.

The increased risk of thromboembolism in pregnancy, and particularly the 6 week period of the puerperium, must be considered (for information on "Pregnancy and lactation" see section 4.6).

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 professional that she is taking a CHC.

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 discoloration 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 CHCs 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 CHC users increases in women with risk factors (see table). [nationally completed name] 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 a CHC should not be prescribed (see section 4.3).

Table: 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 a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	
Obesity (body mass index 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).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use

Migraine	An increase in frequency or severity of migraine during CHC 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 professional that she is taking a CHC.

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.

Tumours

Cervical cancer
In some epidemiological studies an increased risk of cervical cancer has been reported in long term users of COCs, but it is still not clear to which extent this finding may be influenced by impacts of sexual behaviour and other factors, such as human papilloma virus (HPV).

Breast cancer
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 woman 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 below 40 years of age, the excess number of breast cancer diagnoses in current and recent users of COC 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.

Liver tumours
In rare cases, benign and malignant liver tumours have been reported in users of COCs. These tumours have, in isolated cases, lead to life threatening, intra-abdominal haemorrhage. A liver tumour must be taken into consideration as a differential diagnosis when severe pain occurs in the upper abdomen, if there is hepatomegaly, or if there are signs of intra-abdominal haemorrhage in women taking COCs.

Other conditions

Women with hypertriglyceridaemia, or a family history thereof, may be at increased risk of pancreatitis when taking COCs.

In the case of acute or chronic impairment of liver function, the use of [nationally completed name] should be stopped until liver function tests have returned to normal. Steroid hormones may be poorly metabolised in patients with impaired liver function.

Even though slight increases in blood pressure have been reported in many women taking COCs, clinically important increases in blood pressure are rare. If persistent clinical hypertension develops during COC use, intake should be discontinued and the hypertension treated. Use of COCs may be resumed, if appropriate, when normotensive values are reached with antihypertensive therapy.

It has been reported that the following conditions may occur, or worsen both during pregnancy and during use of COCs, but the evidence of a relationship is inconclusive: Jaundice and/or pruritus in connection with cholestasis; development of gallstones; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; loss of hearing due to otosclerosis.

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

COCs may have an influence on the peripheral insulin resistance and glucose tolerance. Therefore, diabetics should be closely monitored during COC use.

Worsening of endogenous depression, of epilepsy (see section 4.5 interactions), of Crohn´s disease and of ulcerative colitis has been reported during COC use.

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.

Chloasma may occur, in particular in women with a medical history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to sunlight or ultraviolet radiation while taking COCs.

Medical examination/consultation

Prior to the initiation or reinstitution of [nationally completed name] 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 contra-indications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of [nationally completed name] 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 user 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.

Reduced efficacy

The efficacy of oral contraceptives may be reduced in the case of missed tablets, gastro-intestinal disturbances (see section 4.2) or concomitant use of other medicinal product (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 during the placebo intake interval. 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.

[nationally completed name] contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

• Effects of other medicinal products on [nationally completed name]

Interactions can occur with medicinal products that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

Management

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 medicinal product therapy enzyme induction may be sustained for about 4 weeks.

Short-term treatment

Women on treatment with enzyme-inducing medicinal products should temporarily use a barrier method or another method of contraception in addition to the COC. The barrier method must be used during the whole time of the concomitant medicinal product therapy and for 28 days after its discontinuation. If the medicinal product therapy runs beyond the end of the active tablets in the COC pack, the placebo tablets must be discarded and the next COC pack should be started right away.

Long-term treatment

In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

The following interactions have been reported in the literature.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.:

Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (hypericum perforatum).

Substances with variable effects on the clearance of COCs:

When co-administered with COCs many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of estrogen or progestins. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional

barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Substances decreasing the clearance of COCs (enzyme inhibitors):

The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Concomitant administration of strong CYP3A4 inhibitors 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.

• Effects of [nationally completed name] on other medicinal products

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

Clinical data suggests that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

Pharmacodynamic interactions

During clinical trials with patients treated for hepatitis C virus infections (HCV) with medicinal products 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 frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see section 4.3).

Therefore, [nationally completed name]-users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these combination medicinal product regimens. [nationally completed name] can be restarted 2 weeks following completion of treatment with these combination medicinal product regimens.

• Laboratory tests
The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal, and renal function; plasma levels of (carrier) proteins, e.g. corticosteroid-binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis, decrease in serum folate levels. Changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Pregnancy

[nationally completed name] is not indicated during pregnancy. If pregnancy occurs during medication with [nationally completed name], the preparation should be withdrawn immediately.

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 pregnancy.

The increased risk of VTE during the postpartum period should be considered when re-starting [nationally completed name] (see section 4.2 and 4.4).

Breast-feeding

Contraceptive steroids can influence breastfeeding, as they can lower the amount and change the composition of breast milk. Small amounts of contraceptive steroids and/or their 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. The use of contraceptive steroids should, therefore, generally not be advised to a breastfeeding mother before her child is completely weaned.

4.7 Effects on ability to drive and use machines

Gestodene/ethinylestradiol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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, which are discussed in more detail in section 4.4.

The most commonly reported ADRs (> 1/10) are irregular bleeding, nausea, weight increase, breast tenderness and headache. They occur usually at the beginning of therapy and are transient.

Organ system class	**Very common (≥1/10)**	**Common (≥1/100 to < 1/10)**	**Uncommon (≥1/1,000 to < 1/100)**	**Rare /10,000 to < 1,000)**	**Very rare (<1/10,000)**	**Unknown (cannot be estimated from the available data)**
Infections and Infestations		Vaginitis, including candidiasis				

Neoplasms benign, malignant, and unspecified					Hepatocellular carcinomas	
Immune system disorders				Anaphylactic/ anaphylactoid reactions, including very rare cases of urticaria and severe reactions with	Exacerbation of systemic lupus erythematosus	Exacerbation of symptoms of hereditary and acquired angioedema**.**
Metabolism and nutrition disorders			Changes in appetite (increase or decrease) Hyperlipidaemia	Glucose intolerance	Exacerbation of porphyria	
Psychiatric disorders		Mood changes, including depression; changes in libido Irritability				
Nervous system disorders	Headache, including migraines	Nervousness, dizziness			Exacerbation of chorea	
Eye disorders		Visual disturbances		Intolerance to contact lenses	Optic neuritis*; retinal vascular thrombosis	

Vascular disorders			Hypertension	Venous thromboembolism, arterial thromboembolism	Aggravation of varicose veins	
Ear and labyrinth				Otosclerosis		
Gastrointestinal disorders		Nausea, vomiting, abdominal pain	Abdominal cramps, bloating		Pancreatitis ischaemic colitis	Inflammatory bowel disease (Crohn's Disease, ulcerative
Hepatobiliary disorder				Cholestatic jaundice	Gallbladder disease, including gallstones**	Hepatocellular injury (e.g. hepatitis, hepatic function abnormal), Cholestasis
Skin and Subcutaneous tissue disorders		Acne	Rash, chloasma (melasma), which may persist, hirsutism, alopecia	Erythema nodosum	Erythema multiforme	
Renal and urinary disorders					Haemolytic uraemic syndrome	

Reproductive system and breast disorders	Breakthrough bleeding/spotting	Breast pain, tenderness, enlargement, secretion; dysmenorrhoea; change in menstrual flow; change in cervical ectropion and secretion; amenorrhoea				
General disorders and		Fluid retention/oedema				
Investigations		Changes in weight (increase or decrease)	Increase in blood pressure; changes in serum lipid levels, including hypertriglyceridaemia	Decrease in serum folate levels***		

* Optic neuritis may lead to partial or complete loss of vision.
** CHCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.
*** Serum folate levels may be depressed by CHC therapy. This may be of clinical significance if the woman becomes pregnant shortly after discontinuing CHCs.

The following serious adverse events have been reported in women using COCs, see sections 4.3 and 4.4.

- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism.
- Arterial thromboembolic disorders
- Liver tumours
- Skin and subcutaneous disorders: chloasma.
- Exacerbation of 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.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No serious harmful effects have been reported with overdoses. Symptoms that can arise in connection with an overdose are: Nausea, vomiting, and vaginal bleeding. There is no antidote, and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormonal contraceptives for systemic use, Progestogens and estrogens, fixed combinations. ATC code: G03 AA10

The overall Pearl index (pregnancies due to method failure + pregnancies due to patient failure) for Ethinylestradiol/Gestodene 30/75 µg is 0.25 (upper limit 95% confidence interval: 0.51). Pearl index for method failure is 0.08 (upper limit 95% confidence interval: 0.29)

The contraceptive effect of COCs is based on the interaction of various factors. The most important of these factors are the inhibition of ovulation and changes in the endometrium.

5.2 Pharmacokinetic properties

Gestodene

Absorption

Gestodene, when taken orally, is absorbed quickly and completely. Following a single dose the maximum serum concentration of 4 ng/ml is reached in approximately one hour. Bioavailability is approximately 99%.

Distribution

Gestodene is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1-2% of the total amount of gestodene in serum is found as free steroid, while 50-70% is specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the distribution of serum proteins, which causes an increase of the SHBG-bound fraction, and a decrease of the albumin- bound fraction. The apparent distribution volume of gestodene is 0.7 l/kg.

Biotransformation

Gestodene is metabolised completely via the known pathways of steroid metabolism. The metabolic clearance rate from serum is 0.8 ml/min/kg. No interaction occurs when gestodene is taken together with ethinylestradiol.

Elimination

Serum level of gestodene is reduced at 2 rates. The last rate is characterised by a half-life of 12 – 15 hours.
Gestodene is not excreted unchanged. Its metabolites are excreted in urine and in bile at a ratio of 6:4. The half-life of metabolite excretion is approximately 1 day.

Pharmacokinetic/pharmacodynamics relationship

Pharmacokinetics of gestodene is influenced by the levels of SHBG in serum, which increase to triple values with ethinylestradiol. Upon daily intake, the level of gestodene in serum increases till approximately four times the single dose value, and reaches steady-state within the second half of the treatment cycle.

Ethinylestradiol

Absorption

Ethinylestradiol, taken orally, is absorbed quickly and completely. Maximal serum concentration of about 80 pg/ml is reached within 1-2 hours. Complete bioavailability, resulting from pre-systemic conjugation and first-pass metabolism, is approximately 60%.

Distribution

During lactation, 0.02% of the daily maternal dose passes into breast milk.
Ethinylestradiol is predominantly bound non-specifically to albumin (approx. 98.5), and causes increase in serum concentration of SHBG. The apparent distribution volume is found to be approximately 5 l/kg.

Biotransformation

Ethinylestradiol undergoes pre-systemic conjugation both in the mucosa of the small intestine, and in the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation, but many different hydroxylated and methylated metabolites are formed, and found as free metabolites and as glucuronide and sulphate conjugates. The metabolic clearance rate is approximately 5 ml/min/kg.

Elimination

Serum level of ethinylestradiol is reduced at 2 rates, the last one with a half-life of 24 hours.
Unchanged Ethinylestradiol is not excreted, but its metabolites are excreted in urine and in bile at a ratio of 4:6. The half-life of metabolite excretion is approximately 1 day.

Pharmacokinetic/pharmacodynamics relationship

Steady-state occurs after 3-4 days, and the serum levels of ethinylestradiol are 30-40% higher than at single dose.

5.3 Preclinical safety data

Ethinylestradiol and gestodene are not genotoxic. Carcinogenicity studies with ethinylestradiol alone or in combination with various progestogens do not indicate any particular carcinogenic hazard to women when used as indicated for contraception. However it should be noted that sex hormones can advance the growth of certain hormone-dependent tissues and tumours.
Reproductive toxicity studies on fertility, development of the fetus or reproductive ability with ethinylestradiol alone or in combination with progestogens revealed no undesirable effects for humans when used as recommended.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active white Tablet:
Lactose monohydrate
Microcrystalline cellulose
Povidone K-30
Magnesium stearate
Polacrilin potassium.

Placebo green tablet:
Lactose monohydrate
Maize starch
Povidone K-30
Magnesium stearate
Silica colloidal anhydrous
Hypromellose 2910
Triacetin (E 1518)
Polysorbate 80
Titanium dioxide (E 171)
FD&C blue 2 aluminium lake (E 132)
Yellow iron oxide (E 172).

6.2 Incompatibilities
Not known

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30ºC. Keep the blister in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Clear to slightly opaque transparent PVC/PVdC-Al blister.

Pack sizes:

28 (21 active plus 7 placebo) tablets

3 x 28 (21 active plus 7 placebo) tablets

6 x 28 (21 active plus 7 placebo) tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Sandoz B.V.
Veluwezoom 22
1327 AH Almere
Nederland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 116281

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 27 januari 2016
Datum van laatste verlenging: 24 november 2020

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 9: 17 mei 2023