SUMMARY OF PRODUCTS CHARACTERISTICS

1. NAAM VAN HET GENEESMIDDEL

Ethinylestradiol/Desogestrel 0,03 mg/0,15 mg Teva, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 micrograms desogestrel and 30 micrograms ethinylestradiol.

Excipients with known effect:
Each tablet contains 58 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
Each tablet is round, white to off-white, 5.00 mm, uncoated, biconvex, debossed with '142' on one side and other side plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception

The decision to prescribe **<Product 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 **<Product name>** compares with other CHCs (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Posology

How to take <Product name>
The tablets must be taken every day at about the same time, if necessary with a little liquid, in the order shown on the blister pack. One tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after a 7-day tablet-free interval; during which time a withdrawal bleeding usually occurs. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

How to start <Product name>

- *No preceding hormonal contraceptive use (in the past month)*

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Tablet intake is also allowed to start on day 2-5, but during the first cycle concurrent use of a barrier method for the first 7 days of tablet intake is advisable.

- *Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring or transdermal patch)*

The woman should start taking **<Product name>** preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or a transdermal patch has been used, the woman should start using **<Product name>** preferably on the day of removal, but at the latest when the next application would have been due. In no case should the hormone-free period of her previous method be extended beyond the recommended duration.

In addition, if the woman has consistently and correctly used her previous combined hormonal contraceptive method during the previous 7 days and it is reasonably certain that she is not pregnant, she may switch to **<Product name>** on any day of the cycle from her previous combined hormonal contraceptive method.

- *Changing from a progestogen-only-method (progestogen-only-pill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)*

The woman may switch any day from the progestogen-only pills (from an implant or the IUS on the day of its removal; from an injectable when the next injection would be due) but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

- *Following first-trimester abortion*

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

- *Following delivery or second-trimester abortion*

For breast-feeding women - see section 4.6.

The woman should be advised **to start** at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days. However if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

Management of missed tablets

If the user is **less than 12 hours** late in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers, and should take further tablets at usual time.

If she is **more than 12 hours** late in taking any tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. tablet-taking must never be discontinued for longer than 7 days

2. 2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamus-pituitary-ovarian-axis.

Accordingly 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 taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the regular tablet-free interval, the higher the risk of a pregnancy.

- *Week 2*

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if she has missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

- *Week 3*

The risk of reduced reliability is imminent because of the forthcoming 7-day tablet-free interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, she should follow the first of these two options and use extra precautions for the next 7 days as well.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next blister pack must be started as soon as the current blister pack is finished, i.e., no gap should be left between packs. The user is unlikely to have a withdrawal bleed until the end of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

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

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

Advice in case of gastro-intestinal disturbances

In case of severe gastro-intestinal disturbances (e.g., vomiting or diarrhoea), 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, under section “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 **<Product name>** without a tablet-free interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of **<Product name>** is then resumed after the usual 7-day tablet-free interval.

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 tablet-free interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

Paediatric population
The safety and efficacy of desogestrel in adolescents below 18 years has not yet been established

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.

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- 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
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Endometrial hyperplasia.
- Known or suspected pregnancy.
- <**Product 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 **<Product 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 **<Product name>** should be discontinued.

Circulatory disorders

Risk of venous thromboembolism (VTE)
The use of any combined hormonal contraceptive 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 <Product 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 <Product 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).

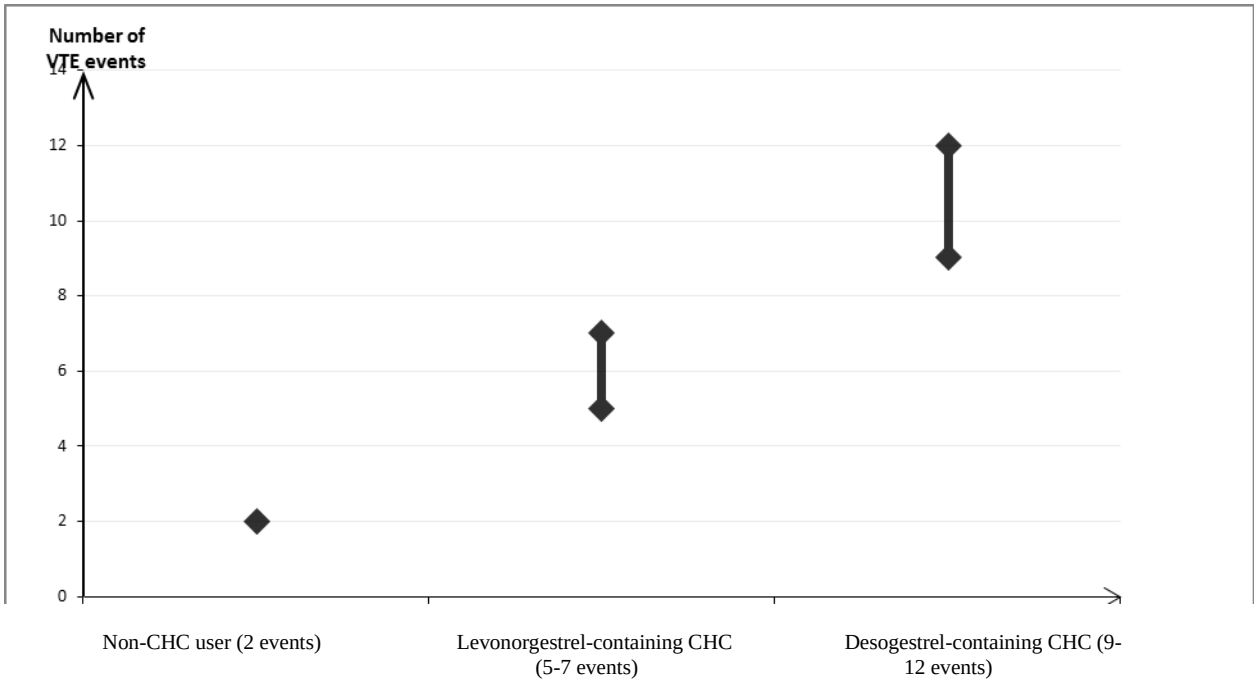
It is estimated[1] that out of 10,000 women who use a CHC containing desogestrel between 9 and 12 women will develop a VTE in one year; this compares with about 6[2] in women who use a levonorgestrel-containing CHC.

[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

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

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 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). **<Product 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 **<Product 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). **<Product 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

Epidemiological studies indicate that the long-term use of oral contraceptives displays a risk factor for the development of cervical cancer in women infected with human papillomavirus (HPV). However, there is still uncertainty about the extent to which this finding is influenced by confounding effects (e.g. differences in number of sexual partners or in use of barrier contraceptives).

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent users of COCs 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 users of COCs, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

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

With the use of the higher-dosed COCs (50 µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dosed COCs remains to be confirmed.

Other conditions

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

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. A systematic relationship between COC use and clinical hypertension has not been established. If, during the use of a COC in preexisting hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

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

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

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regime in diabetics using COCs. However, diabetic women should be carefully observed while taking COC.

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

Worsening of endogenous depression and of epilepsy 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 occasionally occur, especially in women with a medical history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to sunlight or ultra-violet radiation whilst taking COCs.

The above information should be considered when determining the method(s) of contraception.

Medical examination/consultation

Prior to the initiation or reinstitution of **<Product 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 (section 4.3) and warnings (section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of **<Product 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 oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of COCs may be reduced in the event of e.g. missed tablets (section 4.2.), gastro-intestinal disturbances (section 4.2.) or concomitant medication that lower the plasma concentration of ethinylestradiol and/or etonogestrel, the active metabolite of desogestrel (section 4.5.).

Herbal preparations containing St. John's wort (Hypericum perforatum) should not be used while taking **<Product name>** due to the risk of decreased plasma concentrations and reduced clinical effects of **<Product name>** (see section 4.5).

Reduced cycle control

With all COCs, irregular bleeding (spotting and 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 3 cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the tablet-free interval. If 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.

<u>Excipient(s)</u>

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.

Influence of other medical products on <Product name>

Interactions between oral contraceptives and other medicinal products or herbal medicinal products that induce microsomal enzymes, especially the cytochrome P450 enzymes (CYP), which may lead to increased clearance of sex hormones and result in breakthrough bleeding and/or pregnancy.

Management
Enzyme induction can occur after only a few days of treatment. Maximum enzyme induction is generally achieved within a few weeks. After stopping therapy, enzyme induction may continue for up to 4 weeks.

Short-term treatment
Women on treatment with enzyme inducing medicinal products or herbal remedies should temporarily use a barrier method in addition to the COC or choose another method of contraception.
The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

Long-term treatment
For women undergoing long-term treatment with enzyme-inducing drugs, another reliable non-hormonal method of contraception that is not influenced by enzyme-inducing medicinal products is recommended.

The following interactions are known in literature

Substances that increase the clearance of <Product name> (enzyme induction), for example
Phenytoin, phenobarbital, primidone, bosentan, carbamazepine, rifampicin, some HIV protease inhibitors (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz, nevirapine) and possibly also oxcarbazepine, topiramate, rifabutin, felbamate, griseofulvin and products containing the herbal drug St. John's Wort (Hypericum perforatum).

Substances with variable effects on <Product name> clearance
Many combinations of HIV protease inhibitors (e.g. nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine) and/or combinations with hepatitis C virus (HCV) inhibitors (e.g. boceprevir, telaprevir), when co-administered with hormonal contraceptives, may increase or decrease plasma concentrations of progestogens, including etonogestrel or estrogens. In some cases the net effect of these changes may be clinically relevant.

Therefore, the product information of the concomitantly prescribed HIV/HCV medication should be consulted to identify possible interactions and related advice. When in doubt, an additional barrier drug should be used by women treated with protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

Substances that decrease <Product name>'s clearance (enzyme inhibitors)
The clinical relevance of possible interactions with enzyme inhibitors remains unknown.

Concomitant use of strong (e.g. ketoconazole, itraconazole, clarithromycin) or moderate (e.g. fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase plasma concentrations of estrogens or progestogens, including etonogestrel.

Etoricoxib doses of 60 to 120 mg/day showed a 1.4- to 1.6-fold increase in plasma concentrations of ethinylestradiol, respectively, when taken concomitantly with a combined hormonal contraceptive containing 0.035 mg ethinylestradiol.

Influence of <Product name> on other medicinal products

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

Clinical data suggest that ethinylestradiol inhibits the clearance of CYP1A2 substrates, leading to a mild (e.g. theophylline) or moderate (e.g. tizanidine) increase in plasma concentrations of these agents.

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, **<Product 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 drug regimens. **<Product name>** can be restarted 2 weeks following completion of treatment with these combination drug 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. Changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Pregnancy
<Product name> is not indicated during pregnancy.

If pregnancy occurs during the use of **<Product name>**, further intake should be stopped. However, most 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 <Product name> (see section 4.2 and 4.4).

Breast-feeding
Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should generally not be recommended until the breast-feeding mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk, but there is no evidence that this adversely affects infant health.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

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.

As with all COCs, changes in vaginal bleeding patterns may occur, especially during the first months of use. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration.

Possibly related undesirable effects that have been reported in users of **<Product name>**, or COC users in general are listed in the table below[1].
The frequencies of adverse events are ranked according to the following:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

System Organ Class		***Common***	***Uncommon***	***Rare***	***Not known***
Infections and infestations				Vaginal candidiasis	
Immune system disorders				Hypersensitivity	Exacerbation of symptoms of hereditary and acquired angioedema
Metabolism and nutrition disorders			Fluid retention		

Psychiatric disorders		Depressed mood Mood altered	Libido decreased	Libido increased	
Nervous system disorders		Headache	Migraine Dizziness Nervousness		
Eye disorders				Contact lens intolerance	
Ear and labyrinth disorders				Otosclerosis	
Vascular disorders			Hypertension	Thromboembolism (VTE, ATE)	
Gastrointestinal disorders		Nausea Abdominal pain	Vomiting Diarrhoea		
Skin and subcutaneous tissue disorders			Acne Rash Urticaria	Erythema nodosum Erythema multiforme Pruritus Alopecia	
Reproductive system and breast disorders		Breast pain Breast tenderness Irregular bleeding	Amenorrhea Breast enlargement Metrorrhagia	Vaginal discharge Breast discharge	
General disorders and administration site conditions		Weight increased		Weight decreased	

1 The most common appropriate MedDRA term to describe a certain adverse event reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

The following serious adverse events have been reported in women using COCs and are discussed in section 4.4:

- Venous thromboembolic disorders;
- Arterial thromboembolic disorders;
- Hypertension;
- Hormone-dependent tumours (e.g. liver tumours, breast cancer);
- Occurrence or deterioriation of conditions for which an association with OC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, migraine, endometriosis, uterine myoma, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uraemic syndrome, cholestatic jaundice;
- Chloasma;

- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.

The frequency of diagnosis of breast cancer is very slightly increased among OC 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.

Interactions
Breakthrough bleeding and/or reduced reliability may result from interactions of other medicinal products (enzyme inducers) with oral contraceptives (see section 4.5).

Reporting of suspected adverse reactions
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

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations
ATC code: G 03 AA 09

The contraceptive action of COCs is based on interaction of different factors, out of which the most important is the inhibition of ovulation and changes in the cervical secretion. Besides protection against pregnancy, COCs have several positive properties which, next to the negative properties (see sections 4.4 and 4.8), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency.

<Product name> is a COC with ethinylestradiol and the progestogen desogestrel.
Ethinylestradiol is a well known synthetic estrogen.
Desogestrel is a synthetic progestogen. After oral administration it has a strong ovulation-inhibiting activity.
Furthermore, when using the higher-dose COCs (50 µg ethinylestradiol), there is evidence of a reduced risk of fibrocystic mammary tumours, ovarian cysts, pelvic inflammation (PID), ectopic pregnancy and endometrial and ovarian cancer. It remains to be confirmed whether this also applies to the lower-dose COCs.

Paediatric population
No clinical data on efficacy and safety are available in adolescents below 18 years.

5.2 Pharmacokinetic properties

Desogestrel

Absorption
After oral administration of **<Product name>**, desogestrel is rapidly absorbed and converted into etonogestrel. Peak plasma levels are reached after 1.5 hours. The absolute bioavailability is 62-81%.

Distribution
Etonogestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 2-4 % of total serum concentrations are present as free steroid, 40-70 % are specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG affects the distribution among serum proteins, causing an increase in the SHBG-bound fraction and a decrease in the albumin-bound fraction. The volume of distribution of desogestrel is 1.5 l/kg.

Biotransformation
Etonogestrel is completely metabolised by the known routes of steroid metabolism. Serum etonogestrel clearance is approximately 2 ml/min/kg. No interaction has been found with co-administered ethinylestradiol.

Elimination
The serum concentration of etonogestrel decreases in two phases. The terminal elimination phase is characterised by a half-life of approximately 30 hours. Desogestrel and its metabolites are excreted in a urinary/biliary ratio of approximately 6:4.

Steady-State Conditions
The pharmacokinetics of etonogestrel are influenced by SHBG levels, which increase by a factor of 3 under the influence of ethinylestradiol. After daily oral administration, serum levels of etonogestrel increase by a factor of 2-3 and reach an equilibrium concentration (steady state) during the second half of a treatment cycle.

Ethinylestradiol

Absorption
Ethinylestradiol (EE) is rapidly and completely absorbed after oral administration. Maximum serum concentrations of approximately 80 pg/ml are reached within 1-2 hours after administration of a single dose. As a consequence of presystemic conjugation and first-pass metabolism the absolute bioavailability is 60%. The area under the curve and C_{max} may be expected to rise slightly over time.

Distribution
Ethinylestradiol is strongly but not specifically bound to serum albumin (approximately 98.5%) and causes an increase in serum SHBG concentrations. The volume of distribution has been determined to be approximately 5 l/kg.

Biotransformation
Ethinylestradiol undergoes presystemic conjugation both in the small intestine mucosa and in the liver. Ethinylestradiol is mainly metabolised by aromatic hydroxylation, but a large variety of hydroxylated and methylated metabolites are formed and occur as free metabolites or as

glucuronide or sulphate conjugates. Serum clearance of ethinylestradiol is approximately 5 ml/min/kg. In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 and also a mechanistic inhibitor of CYP3A4/5, CYP2C8 and CYPP2J2.

Elimination
The serum concentration of ethinylestradiol decreases in 2 phases; the terminal elimination phase is characterised by a half-life of approximately 24 hours. No unchanged ethinylestradiol is excreted. The metabolites of ethinylestradiol are excreted with a urinary/biliary distribution ratio of approximately 4:6. The half-life for metabolite excretion is approximately 1 day.

Steady-state conditions
Steady-state conditions are obtained after 3 to 4 days, when the serum drug level is approx. 30 to 40% higher than after the administration of a single dose.

5.3 Preclinical safety data

Preclinical data show no special risk for humans when COCs are used according to the instructions. This conclusion is based on conventional repeated dose toxicity studies, genotoxicity studies, carcinogenicity studies and reproductive toxicity studies.
However, it should be remembered that sex hormones can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

all-*rac*-alpha-tocopherol
Potato starch
Povidone K30 (E1201)
Stearic acid (E570)
Silica, colloidal anhydrous (E551)
Lactose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

Clear transparent PVC/PVdC- Aluminium blister of 21 tablets per calender blister strip available in packs containing 1x21, 3x21, 6x21 or 13x21 tablets. Each blister is packed in trilaminated pouch.

Clear transparent PVC/PVdC- Aluminium blister of 21 tablets per calender blister strip available in packs containing 1x21, 3x21, 6x21 or 13x21 tablets. Each blister is packed in trilaminated pouch along with 2g molecular sieve.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Teva Nederland B.V.
Swensweg 5
2031 GA Haarlem
Nederland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 112201

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 6 juni 2013
Datum van laatste verlenging: 1 mei 2018

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft de rubrieken 4.2, 4.4 t/m 4.8 en 5.1 t/m 5.3: 4 december 2023