SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ethinylestradiol/levonorgestrel Teva 0,02 mg/0,1 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.10 mg levonorgestrel and 0.02 mg ethinylestradiol

Excipients with known effect:
Lactose (89 mg/tablet), red aluminium lake (E 129)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Tablets are pink and rounded with the size of approximately 5.7 mm x 3.5 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception

The decision to prescribe <invented 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 <invented name> compares with other combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Posology

How to take <invented name>
Tablets must be taken orally in the order directed on the blister package at about the same time every day, with some liquid if necessary. 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 bleed usually occurs. The bleeding usually starts within 2 to 3 days after the last tablet and may not end before the next pack is started.

How to start <invented name>

- No preceding hormonal contraceptive use (in the past month)
  Tablet-taking is started on day 1 of the woman's natural cycle (= the first day of her menstrual bleeding).

Starting on days 2-5 is allowed but in that case an additional barrier method is recommended for the first 7 days of the first cycle.

- Changing from another combined hormonal contraceptive (COC, vaginal ring, transdermal patch)
  The woman should start with <invented name> preferably on the day after the last hormone-containing tablet of the previous COC, but at the latest on the day following the usual tablet-free break or the last hormone-free tablet of the previous hormonal contraceptive. In case of a vaginal ring or transdermal patch has been used, the woman should start <invented name> preferably on the day of removal, but at the latest when the next application would have been due.

- Changing from a progestogen-only method (oral pill, injection, implant) or intrauterine system (IUS)
  The woman can switch to <invented name> any day from the minipill (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 use an additional barrier method for the first 7 days of tablet-taking.

- Following first-trimester abortion
  The use of the tablets can start immediately. In such a case, no other contraceptive measures are needed.

- Following delivery or second-trimester abortion
  For breast-feeding, see section 4.6.

The use of the tablets is started 21 to 28 days after delivery or second-trimester abortion. When starting later, an additional barrier method must be used for the first 7 days of tablet-taking. If the woman has already had sexual intercourse, pregnancy must be excluded before the actual start of COC use or the woman has to wait for her next menstrual period.

Management of missed tablets
<invented name> contains a very low dose of both hormones, and, as a consequence, the contraceptive efficacy margin is small, if a pill is missed.

If the woman 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 take the next tablets at the usual time.

If she is **more than 12 hours late** in taking any tablet, contraceptive protection may be reduced. The following two basic rules apply in cases where tablets have been missed:

1. Tablet-taking must never be discontinued for longer than 7 days.
2. Adequate suppression of the hypothalamic-pituitary-ovarian-axis requires 7 days of uninterrupted tablet-taking.

Accordingly, the following advice can be given for daily practice:

Week 1

The woman 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 the next tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If the woman has had sexual intercourse in the 7 days before missing the tablet, the possibility of a pregnancy must be considered.
The more tablets have been missed and the closer they are to the regular tablet-free break, the higher the risk of pregnancy.

Week 2

The woman 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 the next 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. If she has not taken the tablets correctly or has missed more than one tablet, she should be advised to use extra contraceptive precautions for the next 7 days.

Week 3

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

1. The woman 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 the next tablets at her usual time. The next pack is started as soon as the current pack is finished, i.e., there is no tablet-free break. There will probably be no withdrawal bleed until the end of the second pack, but the woman may experience spotting or breakthrough bleeding on tablet-taking days.

2. It is also possible to stop taking tablets from the current pack. The woman must then have a tablet-free break of 7 days, including the days she missed tablets, and then continue with the next pack.

If the woman misses several tablets and has no withdrawal bleed during the first normal tablet-free break, the possibility of a pregnancy must be considered.

Advice in case of gastrointestinal disturbances
In case of severe gastrointestinal symptoms, absorption of the active ingredients may not be complete and additional contraceptive measures should be taken.

If vomiting or severe diarrhoea occurs within 3 to 4 hours after taking a tablet, the woman should apply the advice given for missed tablets. If the woman does not want to change her normal tablet schedule, she has to take the extra tablets from another pack.

How to change the starting day of a period or to delay a period

To delay a period, the woman should start a new pack immediately after finishing the current pack without any break. Periods can be delayed as long as wished, but not later than till the end of the second pack. During this time the woman may experience breakthrough bleeding or spotting. Regular intake of <invented name> is then resumed after the usual 7-day tablet-free break.

If the woman wants to change the starting day of her periods to another day of the week, she can be advised to shorten her next tablet-free break by as many days as she likes. The shorter the break, the higher the risk that there will be no withdrawal bleed and that the woman will experience breakthrough bleeding and spotting during the second pack (just as when delaying a period).

Special populations

Children and adolescents
<invented name> is only indicated after menarche.

Geriatric patients
Not applicable. <invented name> is not indicated after menopause.

Patients with hepatic impairment
<invented name> is contraindicated in women with severe hepatic diseases. See also section 4.3

Patients with renal impairment
<invented name> has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

Method of administration
Oral use

4.3 Contraindications
Combined hormonal contraceptives (CHCs) should not be used in the presence of any of the following conditions. Should any of the conditions appear for the first time during CHC use, the use of the product must 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 anti-phospholipid 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
- Severe hepatic disease, current or previous, 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
- Amenorrhoea of unknown cause
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- <invented name> is contraindicated for concomitant use with 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 <invented 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 <invented name> should be discontinued.

Circulatory disorders

Risk of venous thromboembolism (VTE)

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. **The decision to use levonorgestrel/ethinylestradiol should be taken after a discussion with the woman to ensure she understands the risk of VTE with levonorgestrel/ethinylestradiol, 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).

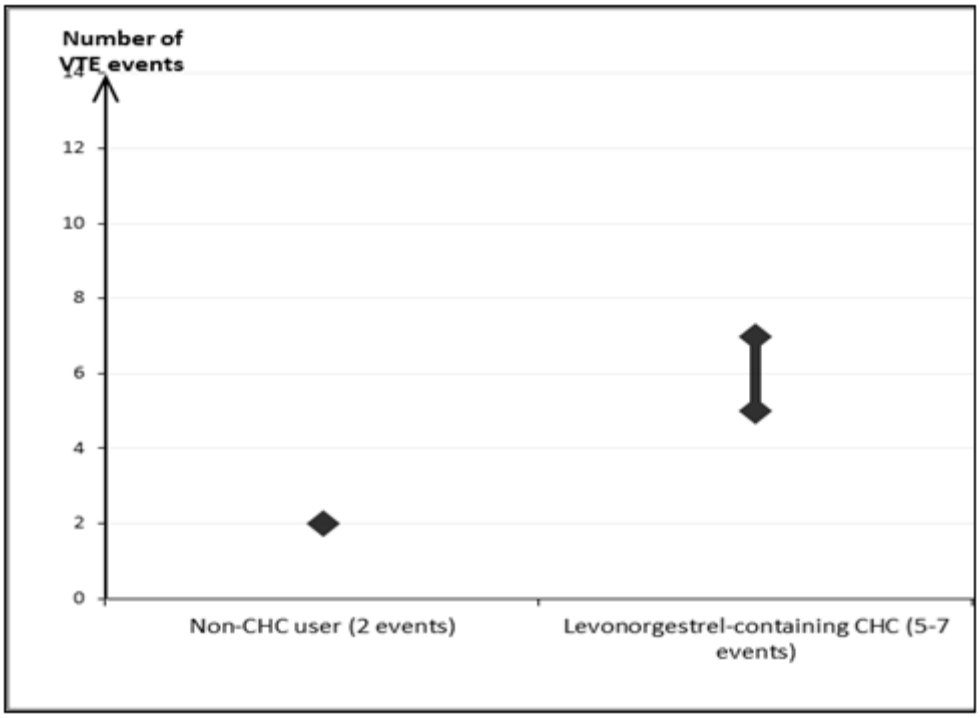
It is estimated that out of 10,000 women who use a CHC that contains levonorgestrel, about 6[1] will develop a VTE in a year.

[1] 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

This number of VTEs per year is fewer than the number expected in women during pregnancy or in the postpartum period.

VTE may be fatal in 1–2% of 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).

Levonorgestrel/ethinylestradiol 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 (BMI) over 30 kg/m^2)	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 pill (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 levonorgestrel/ethinylestradiol 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 "Fertility, 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 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 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). Levonorgestrel/ethinylestradiol 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 (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).	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.

Adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

Tumours

An increased risk of cervical cancer in long-term users of COCs has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

A meta-analysis of 54 epidemiological studies showed that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. This excess risk gradually disappears during the course of 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation.

The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases benign 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 intraabdominal 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.

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 pre-existing 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 during both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis, gallstones; porphyria, systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis and otosclerosis-related hearing loss.

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

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (<0.05 mg ethinylestradiol). However, diabetic women should be carefully monitored, particularly in the early stage of COC use.

Worsening of endogenous depression, of epilepsy, 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 occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

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

Medical examination/consultation

Prior to the initiation or reinstitution of <invented 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 contraindications (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 <invented 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 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 infection (AIDS) and other sexually transmissible diseases.

Reduced efficacy
The efficacy of COCs may be reduced in the event of missed tablets, vomiting or diarrhoea or concomitant medication.

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 period of about three cycles. In users of <invented name>, any bleeding (spotting and/or break-through bleeding) was reported by more than 50% during the first 6 months of use.

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 bleed 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 the COC use is continued.

Excipient(s):

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Red aluminium lake (E129)
It may cause allergic reactions.

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 <invented name>

Interactions can occur with drugs 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 drug therapy enzyme induction may be sustained for about 4 weeks.

Short-term treatment
Women on treatment with enzyme-inducing drugs 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 drug therapy and for 28 days after its discontinuation. If the drug therapy runs beyond the end of the tablets in the COC pack, the next COC pack should be started right after the previous one without the usual tablet-free interval.

Long-term treatment
In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.
Reduced absorption: Drugs that increase gastrointestinal motility, e.g. metoclopramid, may reduce hormone absorption.

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, e.g.:
When co-administered with COCs, many HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV protease 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 for those 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 COCs on other medicinal products
Troleandomycin may increase the risk of intrahepatic cholestasis during coadministration with COCs.
COCs may interfere with the metabolism of other drugs. Increased plasma concentrations of cyclosporin have been reported with concomitant administration of COCs. COCs have been

shown to induce metabolism of lamotrigine resulting in sub-therapeutic plasma concentrations of 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, <invented 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 drug regimens. <invented name> can be restarted 2 weeks following completion of treatment with these drug regimens.

Other forms of interaction

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 blood coagulation and fibrinolysis. The changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Pregnancy
<invented name> is not indicated in pregnancy.

If the woman becomes pregnant while using <invented name>, further intake must be stopped immediately.
However, most epidemiological studies have revealed neither an increased risk of birth defects in children born to women taking contraceptive pills before pregnancy, nor any teratogenic effects at unintentional intake of contraceptive pills in early pregnancy.
The increased risk of VTE during the postpartum period should be considered when re-starting <invented name> (see section 4.2 and 4.4).

Breast-feeding
Lactation may be influenced by contraceptive pills since they may reduce the amount of breast milk and change its composition. Thus, the use of combined oral contraceptives should generally not be recommended until the nursing mother has weaned her child off breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted in breast milk. These amounts may affect the infant.

4.7 Effects on ability to drive and use machines

<invented name> has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most commonly adverse drug reactions with <invented name> are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. They occur in ≥ 1 % to <10% of users.
Serious adverse reactions are arterial and venous thromboembolism.

Tabulated list of adverse reactions
Adverse drug reactions are grouped according to their frequencies. Frequency groups are defined by the following convention: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (frequency cannot be estimated from the available data).
Adverse effects that have been reported in users of combined hormonal contraceptives including <invented name> are:

System organ class	**Frequency of adverse reactions**			
	Common	**Uncommon**	**Rare**	**Not known**
	(≥ 1/100 to < 1/10)	(≥ 1/1,000 to < 1/100)	(≥1/10,000 to < 1/1,000)	cannot be estimated from the available data
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		
Eye disorders			Contact lens intolerance	
Vascular disorders			Arterial thromboembolism (ATE), Venous thromboembolism (VTE)	
Gastrointestinal disorders	Nausea, abdominal pain	Vomiting, diarrhoea		
Hepatobiliary disorders				Transaminases increased
Skin and subcutaneous tissue disorders		rash, urticaria	Erythema nodosum, erythema multiforme	
Reproductive system and breast disorders	Breast tenderness, breast pain	Breast enlargement	Breast discharge, vaginal discharge	
Investigations	Weight increased		Weight decreased	

Red aluminium lake (E 129) may cause allergic reactions.

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.

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of combined oral contraceptives are listed below (see also sections 4.3 and 4.4):

Tumours
- 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.
- Liver tumours (benign and malignant)

Other conditions
- Increased risk of pancreatitis in women with hypertriglyceridemia
- Hypertension
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss
- Liver function disturbances
- Changes in glucose tolerance or effect on peripheral insulin resistance
- Crohn's disease, ulcerative colitis.
- Chloasma

Interactions
Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (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 adverse effects from overdose. Symptoms that may be caused by overdose are nausea, vomiting and withdrawal bleeding. Withdrawal bleeding may even occur in girls before their menarche, if they accidentally take the medicinal product. There are no antidotes and the treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations, ATC code: G03AA07

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 cervical mucus.

Clinical trials have been performed in 2498 women aged 18 to 40 years. The overall Pearl Index calculated from these trials was 0.69 (95 % confidence interval 0.30-1.36) based on 15.026 treatment cycles.

5.2 Pharmacokinetic properties

Levonorgestrel

Absorption
Orally administered, levonorgestrel is absorbed rapidly and completely. Peak serum concentrations of about 2.3 ng/ml are reached about 1.3 hours after taking a <invented name>. The bioavailability is nearly 100 %.

Distribution
Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only 1.1 % of the total serum drug concentrations are present as free steroid, approximately 65 % are specifically bound to SHBG and approximately 35 % are non-specifically bound to albumin. The ethinylestradiol-induced increase in the SHBG concentration influences the relative distribution of levonorgestrel into different protein fractions. Induction of the binding protein causes an increase in the SHBG-bound fraction and a decrease in the albumin-bound fraction. The apparent volume of distribution of levonorgestrel is 129 l after a single dose.

Biotransformation
Levonorgestrel (LNG) is extensively metabolized. The most important metabolic pathways are the reduction of the Δ4-3-oxo group and hydroxylations at positions 2α, 1β and 16β, followed by conjugation. Furthermore, CYP3A4 is involved in the oxidative metabolism of LNG, however, in vitro data suggest that this metabolic route is less relevant than reduction and conjugation. The metabolic clearance rate from serum is approximately 1.0 ml/min/kg.

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

Steady-state
During the continuous use of <invented name>, serum levonorgestrel levels increase about threefold reaching steady-state conditions during the second half of the treatment cycle. Levonorgestrel pharmacokinetics are influenced by the SHBG levels in serum, which are increased 1.5–1.6-fold during the use of estradiol. Therefore, the clearance rate from serum and the volume of distribution are slightly reduced at steady state (0.7 ml/min/kg and about 100 l).

Ethinylestradiol

Absorption
Orally administered ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of about 50 pg/mL are reached within 1-2 hours after taking a <invented name>. During absorption and first-pass hepatic metabolism ethinylestradiol is metabolised extensively, resulting in a mean oral bioavailability of about 45 % (interindividual variation about 20-65 %).

Distribution
Ethinylestradiol is highly (approximately 98 %) but non specifically bound to serum albumin, and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of ethinylestradiol is 2.8–8.6 l/kg.

Biotransformation
Ethinylestradiol is subject to significant gut and hepatic first-pass metabolism. Ethinylestradiol and its oxidative metabolites are primarily conjugated with glucuronide or sulfate. The metabolic clearance rate was reported to be about is 2.3–7 ml/min/kg.
In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2.

Elimination
Ethinylestradiol levels in serum decrease in two phases characterized by half-lives of about 1 hour and 10-20 hours, respectively.
Ethinylestradiol is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of 4:6, and the half-life is about 1 day.

Steady state
Ethinylestradiol concentration in serum increases about twofold after continuous use of <invented name>. Due to the variable half-life of the terminal phase in serum clearance and the daily administration, steady-state conditions are reached within about a week.

5.3 Preclinical safety data

Preclinical studies (general toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction) have not revealed other effects than those which can be explained based on the known hormone profile of ethinyl estradiol and levonorgestrel.

However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Povidone K-30 (E 1201)
Magnesium stearate (E 572)
Opadry II Pink:
- Polyvinyl alcohol
- Talc (E 553b)
- Titanium dioxide (E 171)
- Macrogol (type 3350)
- Red aluminium lake (E 129)
- Lecithin (from soya) (E 322)
- Iron oxide red (E 172)
- Blue aluminium lake (E 132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of the container

Blisters of aluminium push-thru foil and PVC/PVDC film.

It is available in boxes of 1, 3 and 6 packs (blisters), each one containing 21 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

RVG 102388

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 16 december 2009
Datum van laatste verlenging: 26 november 2012

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 3 en 6.1: 15 oktober 2025