SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<invented name> 150 micrograms / 20 micrograms, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

21 white film-coated tablets (active tablets):

Each film-coated tablet contains 150 micrograms of desogestrel and 20 micrograms of ethinylestradiol
Excipients with known effect: Lactose monohydrate 55 mg, soybean oil (maximum 0.026 mg).

7 green placebo (inactive) film-coated tablets:

The tablet does not contain active substances
Excipient with known effect: Lactose monohydrate 55 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Active tablets: White, round film-coated tablets with a diameter of 5 mm approximately. They are coded on one side "C" and on the reverse side "5".
Placebo tablets: Green, round film-coated tablets with a diameter of 5 mm approximately.

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 CHCs (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Route of administration: oral use

How to take <invented 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. Tablet taking is continuous. One tablet is to be taken daily for 28 consecutive days. Each subsequent pack is started the day after the last tablet of the previous pack.

Withdrawal bleeding usually starts on day 2-3 after starting the placebo tablets (last row) and may not have finished before the next strip is started.

Paediatric population
The safety and efficacy of desogestrel and ethinylestradiol in adolescents below 18 years has not yet been established. No data are available.

How to start <invented 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). Starting on day 2-5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

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

The woman should start with <invented 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 <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 (progestogen-only pill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)

The woman may switch any day from the progestogen-only pill (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 needs not to take additional contraceptive measures.

- Following delivery or second-trimester abortion

Women 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.

For breastfeeding women see section 4.6.

Management of missed tablets

Missed pills from the last row of the blister are placebo tablets and thus can be disregarded. However, they should be discarded to avoid unintentionally prolonging the placebo tablet phase.
The following advice only refers to missed active tablets (rows 1-3 of the blister):

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

Accordingly the following advice may 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 2 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 placebo tablets phase, 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 2 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 placebo tablet phase. 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 until the active tablets are used up. The 7 tablets from the last row (placebo tablets) must be discarded. The next blister strip must be started right away. The user is unlikely to have a withdrawal bleed until the end of the active tablets section 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 active tablet-taking from the current blister pack. She should then take tablets from the last row (placebo tablets) for 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 placebo tablet phase, 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 be not complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after active 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 withdrawal bleed

To delay a period the woman should continue with another blister pack of <invented name> without taking the placebo tablets from her current pack. The extension can be carried on for as long as wished until the end of the active tablets in the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of <invented name> is then resumed after the placebo tablet phase.

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 placebo tablet phase 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).

4.3 Contraindications

Combined oral contraceptives (COCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during COC 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

- 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).
- Endometrial hyperplasia.
- Undiagnosed vaginal bleeding.

- Hypersensitivity to the active substances of <invented name> or to any of the excipients listed in section 6.1.
- If you are allergic to peanut or soya.

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. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as <invented 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 <invented 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.**

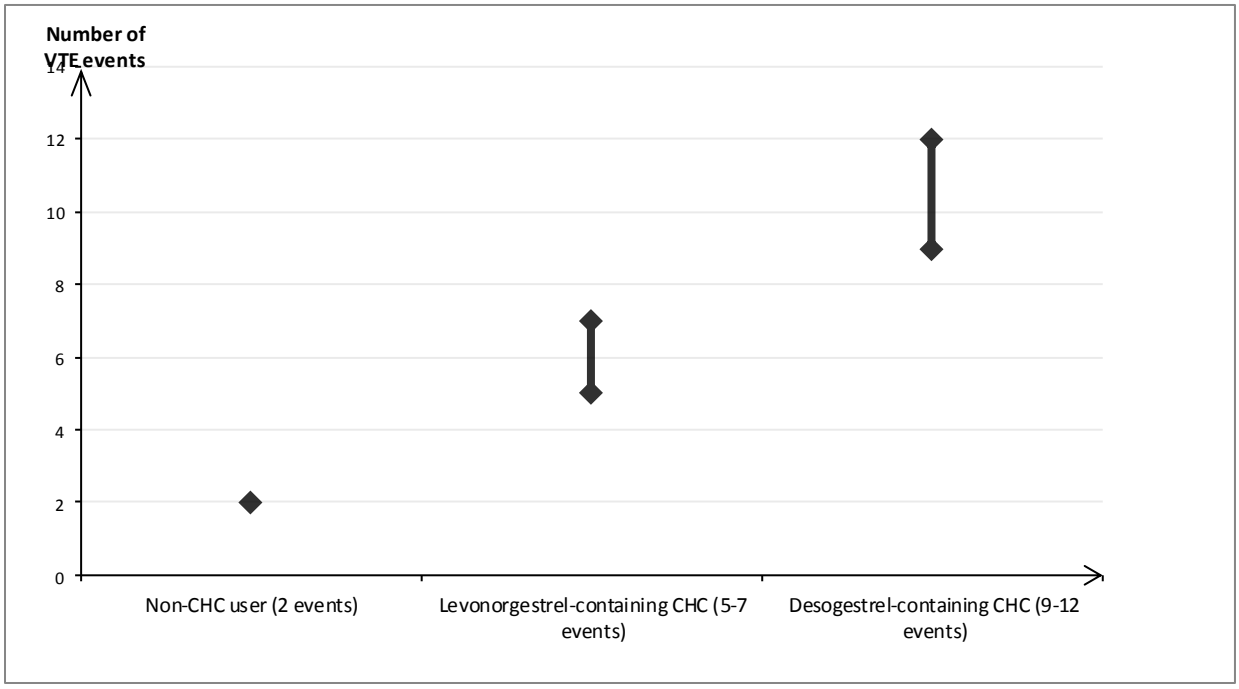
In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

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.

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 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.

<u>Risk factors for VTE</u>

[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

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).

<invented 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 <invented 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). <invented 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.

Occurrence of one or more of these symptoms may be a reason for immediate discontinuation of <invented name> usage.

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

The increased risk of thromboembolism in the puerperium must be considered (for information on "Pregnancy and lactation" see Section 4.6).

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

Tumours

- Epidemiological studies indicate that the long-term use (> 5 years) 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 to 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 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 cancer diagnosed in ever-users tends 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. A systematic relationship between COC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. 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; (hereditary) angioedema.

- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.
  Recurrence of cholestatic jaundice and/or cholestasis-related pruritis which occurred first 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 regimen in diabetics using COCs (containing <0.05 mg ethinylestradiol). However, diabetic women should be carefully observed while taking COCs.

- Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC use.

- 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.

- Each white tablet of this medicinal product contains 55 mg lactose per tablet, each green tablet contains 55 mg. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

When counselling the choice of contraceptive method(s), all the above information should be taken into account.

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 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 <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 to the advice given. The frequency and nature of further periodic checks 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 4.2.3), gastro-intestinal disturbances (Section 4.2.4) or concomitant medication (Section 4.5.1).

Herbal preparations containing St. John's Wort (Hypericum perforatum) should not be used while taking <invented name> due to the risk of decreased plasma concentrations and reduced clinical effect of <invented name> (see Section 4.5. Interactions with other medicinal products and other forms of interaction).

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 tablet 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 the 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.

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 <invented name>

Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or oral contraceptive failure. The following interactions have been reported in the literature:

Hepatic metabolism:
Interactions can occur with drugs that induce microsomal enzymes, which can result in increased clearance of sex hormones (eg. hydantoins, barbiturates, primidone, bosentan, carbamazepine, rifampicin, rifabutin, and possibly also oxcarbazepine, modafinil, topiramate, felbamate, ritonavir, griseofulvin and products containing St John's wort). Also HIV protease inhibitors with an inducing potential (e.g. ritonavir and nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine and efavirenz), may affect hepatic metabolism. Maximal enzyme induction is generally not seen for 2-3 weeks but may then be sustained for at least 4 weeks after the cessation of drug therapy.

Interference with the enterohepatic circulation
Contraceptive failures have also been reported with antibiotics, such as ampicillin and tetracyclines. This mechanism of this effect has not been elucidated.

Management
Women on treatment with any of the above-mentioned classes of medicinal products, should temporarily use a barrier method in addition to the COC, i.e. during the time of concomitant medicinal product administration and for 7 days after their discontinuation.
For women on rifampicin, the barrier method should be used during the time of concomitant drug administration and for 28 days after they discontinuation.
In case of long-term treatment with microsomal enzyme-inducing drugs another method of contraception is recommended.
If concomitant medicinal product administration runs beyond the end of the active tablets in the COC pack, the next COC pack should be started without the usual placebo tablet interval.

Influence of <invented name> on other medicinal products

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

Laboratory analyses
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
<Invented name> is not indicated during pregnancy. If pregnancy occurs during the treatment with <invented 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 where taken inadvertently during 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).

Breastfeeding

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 nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk. These amounts may affect the child.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of COCs.

4.8 Undesirable effects

For serious adverse effects in users of COCs see section 4.4.

The following adverse drug reactions have been reported during use of <invented name>:

System Organ Class	Very Common (>1/10)	Common / Uncommon (≥1/1,000 to <1/10)	Rare (<1/1,000)
Infections and infestations			Vaginal candidiasis
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders		Fluid retention	
Psychiatric disorders		Depressed mood Altered mood Libido decreased	Libido increased
Nervous system disorders		Headache Dizziness Nervousness	
Eye disorders			Contact lens intolerance
Ear and labyrinth disorders			Otosclerosis
Vascular disorders		Migraine Hypertension	Venous or arterial thromboembolism
Gastrointestinal disorders		Nausea Abdominal pain Vomiting	
Skin and subcutaneous tissue disorders		Acne Rash Urticaria	Erythema nodosum Erythema multiforme Pruritus Alopecia
Reproductive system and breast disorders	Irregular bleeding	Amenorrhea Breast tenderness Breast pain Breast hypertrophy Metrorrhagia	Vaginal discharge Breast discharge
General disorders and	Weight increase		

administration site conditions			

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.

A number of undesirable effects have been reported in women using combined oral contraceptives, which are discussed in more detail in section 4.4 Special Warnings and Precautions for Use:

- Hypertension;
- Hormone-dependent tumours (e.g. liver tumours, breast cancer);
- Occurrence or deterioration of conditions for which an association with COC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, endometriosis, uterine myoma, porphyria, systemic lupus erythematosus, gestational 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.
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

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.

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 {to be completed nationally}*.

4.9 Overdose

There have been no reports of serious, harmful effects after overdose.
On the basis of general experience with combined oral contraceptives, symptoms that may possibly occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding. There is no antidotes, and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations.
ATC Code: G03A A09.

The contraceptive effect of COCs is based on interaction of various factors, the most important of which are seen as the inhibition of ovulation and changes in the cervical secretion.

<invented 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.

In the largest multicenter trial (n=23 258 cycles), the uncorrected Pearl Index is estimated at 0.1 (95% confidence interval 0.0-0.3). Furthermore, 4.5% of the women reported absence of withdrawal bleeding and 9.2% reported occurrence of irregular bleeding after 6 treatment cycles.

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 <invented name>, desogestrel is rapidly absorbed and converted into 3-keto-desogestrel. Peak plasma levers of approx. 2 ng/ml are reached at about 1.5 hours after a single dose administration. The absolute bioavailability of 3-keto-desogestrel is 62-81 %.

Distribution

3-keto-desogestrel is bound to serum albumin and SHBG. The ethinyl-oestradiol-induced increase in SHBG influences both the amount of bindings and distribution of 3-keto-desogestrel in the plasma proteins. As a consequence the concentration of 3-keto-desogestrel rises slowly during treatment until steady state is reached within 3-13 days.

Biotransformation

The phase-I metabolism of desogestrel includes cytochrom P-450 catalysed hydroxylation and subsequent dehydrogenation at C3. The active metabolite of 3-keto-desogestrel is further reduced, the degradation products are conjugated to sulphate and glucuronides. Animal studies indicate that the enterohepatic circulation has no relevance for the gestagenic activity of desogestrel.

Elimination

3-keto-desogestrel is eliminated with a mean half-life of approx.31 hours (24-38 hours), plasma clearance varies from 5.0-9.5 l/hours. Desogestrel and its metabolites are eliminated via the urine and in the faeces, either as free steroids or conjugates. Ratio for elimination in urine or faeces is 1.5:1.

Steady-State conditions

In steady-state conditions the serum level of 3-keto-desogestrel is elevated by two- to threefold.

Ethinylestradiol

Absorption

Ethinylestradiol is rapidly absorbed and peak and peak plasma levers of about 80 pg/ml are reached after 1.5 hours after a single dose administration. As a consequence of presystemic conjugation and first-pass metabolism the absolute bioavailability is 60%. The area under the curve and Cmax may be expected to rise slightly over time.

Distribution

Ethinylestradiol is 98.8% bound to the plasma proteins, almost exclusive to albumin.

Biotransformation

Ethinylestradiol undergoes presystemic conjugation both in the mucosa of the small intestine and in the liver. Hydrolysis of the direct conjugates of ethinylestradiol with the aid of the intestinal flora gives ethinylestradiol, which can be re-absorbed, and an enterohepatic circulation in hereby set up. The primary pathway of ehinylestradiol metabolism is cytocrom P-450-mediated hydroxylation in which the primary metabolites are 2-OH-EE and 2-methoxy-EE. 2-OH-EE is further metabolized to chemically reactive metabolites.

Elimination

Ethinylestradiol disappears from plasma with a half-life of approximately 29 hours (26-33 hours), plasma clearance varies from 10-30 l/hour. The conjugates of ethinylestradiol and its metabolites are excreted via urine and faces (ratio 1:1).

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

Toxicological studies have not revealed other effects than those, which can be explained, based on the hormone profile of <invented name>.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active film-coated tablets (white):

- **Tablet core:**
  Lactose monohydrate
  Maize starch
  Povidone K-30 (E1201)
  RRR-Alpha-tocopherol (E307)
  Soybean oil
  Silica colloidal hydrated (E551)
  Silica colloidal anhydrous (E307)
  Stearic acid (E570)

- **Tablet film-coating:**
  Hypromellose 2910 (E464)
  Macrogol 400
  Titanium dioxide (E171)

Placebo film-coated tablets (white):

- **Tablet core:**
  Lactose monohydrate
  Maize starch
  Povidone K-30 (E1201)
  Silica colloidal anhydrous (E551)
  Magnesium stearate (E572)
- **Tablet film-coating**:
  Hypromellose 2910 (E464)
  Triacetin (E1518)
  Polysorbate 80
  Titanium dioxide (E171)
  FD & C Blue 2 Aluminium lake (E132)
  Yellow Iron Oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.3 Special precautions for storage

Do not store above 30ºC. Store in the original package in order to protect from light.

6.4 Nature and contents of the container

Blisters of aluminium push-thru foil and clear to slight opaque PVC/PVDC film.

Pack sizes:
1 x 21+7 film-coated tablets (21 active tablets plus 7 placebo tablets)
3 x 21+7 film-coated tablets (21 active tablets plus 7 placebo tablets)
6 x 21+7 film-coated tablets (21 active tablets plus 7 placebo tablets)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

8. MARKETING AUTHORISATION NUMBERS

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]