SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<invented name> 0.150 mg / 0.030 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.150 mg of desogestrel and 0.030 mg of ethinylestradiol
Excipient with known effect: Lactose monohydrate 55 mg, soybean oil (maximum 0.026 mg)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White, round film-coated tablets of 5.00 mm diameter.

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. 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. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

Paedriatic population
The safety and efficacy of desogestrel 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).

- Changing from another combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or 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 need not 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

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 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 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 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 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 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 2 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, 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 pack.

How to postpone a withdrawal bleed

To delay a period the woman should continue with another blister pack of <invented 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 <invented 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).

4.3 Contraindications

Combined ~~oral~~hormonal contraceptives (C~~H~~HOCs) should not be used in ~~the presence of any of~~ the following conditions ~~listed below~~. Should any of the conditions appear for the first time during C~~H~~HOC use, the product should be stopped immediately.

- ~~Presence or history of venous thrombosis (deep venous thrombosis, pulmonary embolism).~~
- ~~Presence or history of arterial thrombosis (myocardial infarction, cerebrovascular accident) or prodromal conditions (e.g. transient ischemic attack, angina pectoris).~~
- ~~Known predisposition for venous or arterial thrombosis, such as Activated Protein C (APC) resistance, antithrombin III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, and antiphospholipid antibodies.~~
- ~~Recent severe or history of recurrent migraine both with focal neurological symptoms (see section 4.4.1).~~
- ~~Diabetes mellitus with vascular involvement.~~
- ~~The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see section 4.4.1).~~
- 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)
- Endometrial hiperplasia.
- 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

4.4.1 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.

~~If any of the conditions/risk factors mentioned below is present, the benefits of COC use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether COC use should be discontinued.~~

1. 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.**

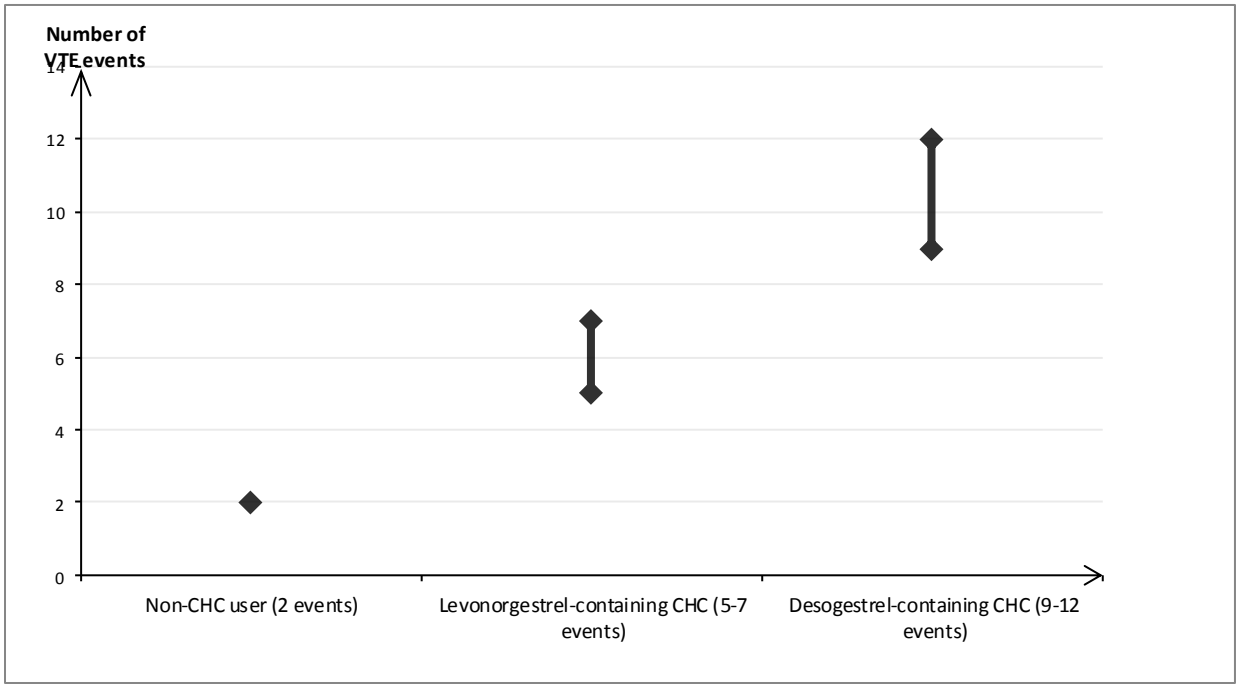
In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

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



[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

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).

<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

Risk factor	Comment
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.

- The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The incidence of VTE is considered to be 5-10 per 100,000 women years in non-OC users. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. The risk of VTE associated with pregnancy is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2% of cases.

- In several epidemiological studies it has been found that women using combined oral contraceptives with ethinylestradiol, mostly with a dose of 30µg, and a progestin such as desogestrel have an increased risk of VTE compared with those using combined oral contraceptives containing less than 50 µg of ethinylestradiol and the progestin levonorgestrel.

- For brands containing 30 µg ethinylestradiol combined with desogestrel or gestodene compared with those containing less than 50 µg ethinylestradiol and levonorgestrel, the overall relative risk of VTE has been estimated to range between 1.5 and 2.0. The incidence of VTE for levonorgestrel containing combined oral contraceptives with less than 50 µg of ethinylestradiol is approximately 20 cases per 100,000 women years of use. For <invented name> the incidence is approximately 30-40 cases per 100,000 women years of use: i.e. additional 10-20 cases per 100,000 women years of use. The impact of the relative risk on the number of additional cases would be greatest in women during the first year they ever use a combined oral contraceptive when the risk for VTE with all combined oral contraceptives is highest.

- The risk of venous thromboembolism increases with:
  - increasing age;
  - a positive family history (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use;
  - obesity (body mass index over 30 kg/m^2);
  - prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilization.

- and possibly also with superficial thrombophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the etiology of venous thromboembolism.

- The use of COCs in general has been associated with an increased risk of acute myocardial infarction (AMI) or stroke, a risk that is strongly influenced by the presence of other risk factors (e.g. smoking, high blood pressure, and age) (see also below). These events occur rarely. It has not been studied how <invented name> modifies the risk of AMI.

- The risk of arterial thromboembolic complications increases with:
  - increasing age;
  - smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
  - dyslipoproteinaemia;
  - obesity (body mass index over 30 kg/m^2);
  - hypertension;
  - migraine;
  - valvular heart disease;
  - atrial fibrillation;
  - a positive family history (i.e. arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.

- Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

- Symptoms of venous or arterial thrombosis can include: unilateral leg pain and/or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; "acute" abdomen. 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.

RMS assessment:
The information above is already included in the tables with riskfactors for VTE and ATE. Therefore, the MAH is requested to delete this information.

- 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.

RMS assessment:

The information above is already included in the tables with riskfactors for ATE. Therefore, the MAH is requested to delete this information.

- ~~Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).~~

- When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than the risk associated with COC use.

~~1.~~2. *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 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 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.

~~2.~~3. *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 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 pruritis 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 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. However, diabetic women should be carefully observed while taking COCs.

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

- <invented name> contains lactose (55 mg). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on 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.

4.4.2 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 ~~if clinically indicated~~ 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 transmissible diseases.

4.4.3 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 effects of <invented name> (see Section 4.5 Interactions).

4.4.4 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 previous 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.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Interactions

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 (e.g., 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.

Contraceptive failures have also been reported with antibiotics, such as ampicillin and tetracyclines. The mechanism of this effect has not been elucidated.

Women on treatment with any of these drugs should temporarily use a barrier method in addition to the COC, or choose another method of contraception.With microsomal enzyme-inducing drugs, the barried method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. In case of long-term treatment with microsomal enzyme-inducing drugs another method of contraception should be considered. Women on treatment with antibiotics (except rifampicin and griseofulvin, which also act as microsomal enzyme-inducing drugs) should use the barrier method until 7 days after discontinuation. If the period during which the barrier method is used runs beyond the end of the tablets in the COC pack, the next COC pack should be started without the usual tablet free interval.

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).

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

4.5.2 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 usually remain within the normal laboratory reference values.

4.6 Fertility, pregnancy and lactation

Pregnancy

<Invented name> is not indicated during pregnancy. If pregnancy occurs during 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 were 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, but there is no evidence that this adversely affects infant health.

4.7 Effects on ability to drive and use machines

<Invented name> has no influence on the ability to drive and use machines.

4.8 Undesirable effects

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

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

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders		Fluid retention	
Psychiatric disorders	Depressed mood Altered mood	Libido decreased	Libido increased
Nervous system disorders	Headache	Migraine	

Eye disorders			Contact lens intolerance
Vascular disorders		Hypertension	Venous or arterial t~~T~~hromboembolism
Gastrointestinal disorders	Nausea Abdominal pain	Vomiting Diarrhoea	
Skin and subcutaneous tissue disorders		Rash Urticaria	Erythema nodosum Erythema multiforme
Reproductive system and breast disorders	Breast pain Breast tenderness	Breast enlargement	Vaginal discharge Breast discharge
General disorders and administration site conditions	Weight increase		Weight decreased

Description of selected adverse reactions

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

The 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;
- Liver tumours;
- Occurence 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.

4.9 Overdose

There have been no reports of serious, harmful effects after overdose. The symptoms which may occur in this case are: nausea or vomiting, and in young girls, a slight vaginal bleeding. There is no antidote, 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

Orally administered desogestrel is rapidly and completely absorbed and converted to etonogestrel. Peak serum concentrations of approx. 2 ng/ml are reached at about 1.5 hours after a single dose administration. Bioavailability is 62-81 %.

Distribution

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

Biotransformation

Etonogestrel is completely metabolized is completely metabolized by the metabolic pathways known to steroids. The metabolic clearance rate from serum is about 2 ml/min/kg. No interaction with concomitant ethinylestradiol administration has been found.

Elimination

Etonogestrel serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 30 hours. Desogestrel and its metabolites are extracted at a urinary to biliary ratio of about 6:4.

Steady-State conditions

Etonogestrel pharmacokinetics are influenced by SHBG levels, which are increased by 3 times with ethinylestradiol. With daily administration, serum concentrations of etonogestrel increase approximately 2 to 3 times, reaching a steady state during the second half of the treatment cycle.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 80 pg/ml are reached within 1-2 hours after a single dose administration. Absolute bioavailability as a result of pre- sytemic conjugation and first pass metabolism is approximately 60%.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5 l/kg was determined.

Biotransformation

Ethinylestradiol is subject to pre-systemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucoronides and sulphate. The metabolic clearance rate is about 5 ml/min/kg.

Elimination

Ethinylestradiol serum levels decrease in two phases, the terminal elimination phase is characterised by a half-life of approximately 24 hours. Unchanged drug is not excreted; ethinylestradiol metabolites are excreted at urinary to biliary ratio of approx. 4:6. The half-life of metabolite excretion is about 1 day.

Steady-State Conditions

Steady state concentrations are reached after 3-4 days when serum drug levels are higher by 30-40% compared to single dose.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Nevertheless, it must be taken into account that sexual steroids may stimulate some tissue and tumours hormone-dependent growth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- **Tablet core:**
  Lactose monohydrate
  Maize starch
  Povidone K-30 (E1201)
  d-Alpha-tocoferol (E307)
  Soybean oil
  Silica colloidal hydrated (E551)
  Silica colloidal anhydrous (E551)
  Stearic acid (E570)
- **Tablet film-coating:**
  Hypomellose 2910 (E464)
  Triacetin (E1518)
  Polysorbate
  Titanium dioxide (E171)

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 21film-coated tablets
3 x 21 film-coated tablets
6 x 21 film-coated 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 NUMBER(S)

[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]