Summary of product characteristics

<Invented Name>

0.03 mg/2.0 mg coated tablets

1. Name of the medicinal product

<Invented Name>

0.03 mg/2.0 mg coated tablets.

2. Qualitative and quantitative composition

Active ingredient: Ethinylestradiol, Dienogest

1 coated tablet contains:

Ethinylestradiol	0.03 mg
Dienogest	2.0 mg

Excipients with known effect: lactose monohydrate (60.90 mg),

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet

White, round film-coated tablets. Approx. 5.0 mm of diameter

4. Clinical particulars

4.1 Therapeutic indications

- Hormonal contraception.

- Treatment of women with moderately severe acne, with no contraindications for therapy with oral contraceptives and after failure of suitable topical treatments

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

4.2.1 Posology and method of administration

One tablet of **<Invented Name>** daily for 21 consecutive days.

The tablets should be taken at approximately the same time of the day each day, if necessary with some liquid.

The first tablet to be taken is the one that corresponds to the day of the week in which the medication is started as written in the blister pack (e.g. "Mo" for Monday).

The rest of the intake is done the in arrow direction, until the blister pack is consumed.

After the first 21 tablets have been taken, a break is made for 7 days. Two to four days after the last tablet, a withdrawal bleed typically begins.

Whether or not a bleed has occurred, the new blister pack is initiated after the 7 treatment-free days.

The contraceptive protection also occurs during the 7-day intake pauses.

4.2.2 Beginning of the intake of **<Invented Name>**

• No previous use of hormonal contraception in the past month:

The first day of the cycle (first day of the menstruation) will begin with the intake. When taken correctly, contraception starts on the first day of dosing.

If the intake starts between days 2 and 5, during the first 7 days of the tablet-taking a non-hormonal method of contraception (barrier methods) should be additionally used.

• Switching from another combination compound to hormonal contraception (combined oral contraceptive, vaginal ring, transdermal patch):

Depending on the type of the previously combined oral contraceptive, the intake of <Invented Name> should start either the day after the usual tablet-free interval, following the use of the last active tablet, or the day after the intake of the last placebo tablet of the previously completed combined oral contraceptive. If a transdermal patch or a vaginal ring was used before, then, the intake of **<Invented Name>** should start the day after the usual ring-free or patch-free interval.

• Switching from a progestogen-only method (mini-pill, implants, injectable forms) or from an intrauterine device:

If the mini-pill has been taken before, the switch can be made any day; the conversion from an implant or an intrauterine device has to happen on the day of the removal; and for an injection compound, at the moment when the next injection is due. In any case, during the first 7 days of the intake of **<Invented Name>**, it is necessary to use a non-hormonal protection method (barrier method).

• After an abortion in the first trimester, the intake of **<Invented Name>** can be started immediately. In this case, no additional contraceptive measures are necessary.

• After birth or an abortion in the second trimester (for use during the lactation period, see section 4.6).

Since in the period immediately following childbirth, the risk of thromboembolic events is increased, the intake of oral contraceptives should not be started until 21 to 28 days after childbirth for non-lactating mothers or after an abortion in the second trimester. During the first 7 days of intake, a non-hormonal contraceptive method (barrier method) should be additionally used. If intercourse has already taken place, pregnancy should be excluded or it is necessary to wait until the first spontaneous menstruation before beginning to take the medication.

4.2.3 Duration of use

<Invented Name> can be used as long as a hormonal method of contraception is desired, and if no health risks are posed (for regular control exams, see section 4.4.4).

4.2.4 Management of missed doses

The contraceptive effect of **<Invented Name>** can be reduced if it is not taken regularly.

If the intake is missed once, but resumed within 12 hours from the usual intake time, the contraceptive effect is not affected. All following tablets should be taken again at the usual time.

If the tablet is taken more than 12 hours after the usual intake time, the contraceptive effect can no longer be guaranteed. The probability of pregnancy becomes higher the closer the forgotten tablet is to the tablet-free interval.

If the usual withdrawal bleed does not occur following the forgotten dose, pregnancy should be excluded until a new blister pack is started.

The two following rules apply in case of missing to take the tablet:

1. The intake of the tablet should not be interrupted for longer than 7 days.

2. A regular intake of the tablets for at least 7 days is necessary to effectively eliminate the hypothalamus-hypophyseal-ovary axis.

In case of missed tablets, the management is as follows:

The intake of the last missed tablet should be resumed as soon as possible, even if this means taking 2 tablets in one day. Then, the further tablet intakes take place at the usual time. Additionally, a non-hormonal contraceptive method should be used for the next 7 days.

If the tablet is missed only once in the second week there is no need to use additional contraceptive methods.

If more than one tablet is missed, until the occurrence of the next withdrawal bleed, a non-hormonal contraceptive method should be additionally used.

1. If there are less than 7 days between the missed tablet and the last tablet of the current blister pack, the next blister pack should be started immediately (no intake pause) on the day after

taking the last tablet of this blister pack. Probably there will be no usual withdrawal bleed until this second blister pack is finished. But there can be cumulative breakthrough bleedings or instances of spotting.

2. Alternatively the intake of more tablets from the current blister pack can be interrupted and the tablet-free interval can be advanced in time. After the tablet-free interval of up to 7 days, including the days of the missed tablets, the tablet-intake of next blister pack can be continued.

4.2.5 Management in case of vomiting or diarrhea

In case of vomiting or severe diarrhea within the first 4 hours of intake of **<Invented Name>**, the active ingredient may not be fully absorbed and additional contraceptive measures should be used. Moreover, the same instructions apply as in the one-time missed tablet (see also section 4.2.4). If the usual intake schedule is to be maintained, additional tablets from another blister pack have to be taken. In case of persistent or recurring gastrointestinal problems, non-hormonal contraception methods should be additionally used and the doctor should be informed.

4.2.6 Postponement of the Withdrawal Bleed

To postpone the withdrawal bleed, the user should continue to take the tablets from the next blister pack of <Invented Name> directly, with no tablet-free interval. The withdrawal bleed can be postponed as much as desired, but only until the second blister pack is finished. For that period, breakthrough bleedings or instances of spotting can occur. After the following usual 7-day tablet-free interval, the intake of **<Invented Name>** can continue as usual.

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following conditions.

- 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

- Smoker (see section 4.4)..

- Presence or history of pancreatitis, if it is associated with severe hypertriglyceridemia.

- Presence or history of hepatic disease, as long as liver function values have not returned to normal (also Dubin-Johnson and Rotor Syndrome).

- Presence or history of liver tumors.

- Known or suspected malignant conditions of the genital organs (e.g. in the breast or in the endometrium)

- Undiagnosed vaginal bleeding.

- Undiagnosed amenorrhea.

- Hypersensitive to any of the active substances or to any of the excipients.

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.

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. It is not yet known how the risk with [invented name] compares with these lower risk products. The decision to use any product other than one known to have the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with CHCs, 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).

Epidemiological studies in women who use low dose combined oral contraceptives (<50 μg ethinylestradiol) have found that out of 10,000 women between about 6 to 12 will develop a VTE in one year.

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

Limited epidemiological data suggest that the risk of VTE with dienogest-containing CHCs may be similar to the risk with levonorgestrel-containing CHCs.

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.

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

[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

	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.

Patients with rare hereditary problems of fructose intolerance, galactose intolerance, lactase deficiency, sucrose-isomaltase deficiency, or glucose-galactose malabsorption should not take <Invented Name>.

4.4.1 Reasons for the immediate termination of the **<Invented Name>** intake (in addition to the contraindications given in 4.3):

- Known or suspected pregnancy.

- First signs of venous inflammation or signs of a possible thrombosis (including retinal thrombosis), embolism or myocardial infarction (see section 4.4.3.1).

- Constantly elevated blood pressure levels at above 140/90 mmHg. The resume of the combined oral contraceptive intake can be considered as soon as the blood pressure values are normalized under anti-hypertensive treatment.

- Planned operation (at least 4 weeks in advance) and/or long immobilization (e.g. after accidents). The intake should be resumed no earlier than 2 weeks after the complete remobilization.

- First occurrence or deterioration of a migraine.

- If headaches occur with unusual frequency, duration or intensity, or if focal neurological symptoms suddenly appear (possible first sign of a stroke).

- Strong upper abdomen pain, liver increase or signs of an intraabdominal bleeding (possible indications of a liver tumor, see section 4.4.3.2).

- Occurrence of jaundice, hepatitis, generalized pruritus, cholestasis, and abnormal liver function values. In case of limited liver function, steroid hormones are less metabolized.

- Acute diabetes mellitus.

- New or recurrent porphyria.

4.4.2 Conditions / risk factors requiring special medical attention:

- Heart and kidney diseases, since the active substance ethinylestradiol can cause liquid retention.
- Superficial phlebitis, strongly marked tendency to varicosis, peripheral breakthrough bleeding problems, since they can be associated with the occurrence of thrombosis.
- Blood pressure increase (to over 140/90 mmHg).
- Lipometabolism problems. In users with lipometabolism, ethinylestradiol of the estrogen proportion in **<Invented Name>** can cause steep increases in plasma triglycerids and subsequently pancreatitis and other complications (see also section 4.3).
- Sickle cell anemia.
- History of hepatic diseases.
- Gall bladder diseases.
- Migraine.
- Depression. It must be clarified whether the depression is linked to the use of **<Invented Name>**. If necessary, other, non-hormonal contraception methods should be used.
- Reduced glucose tolerance/diabetes mellitus. Since combined oral contraceptives can affect peripheral insulin resistance and glucose tolerance, the necessary dosage of insulin or other diabetes medication can possibly change.

- Smoking (see section 4.4.3).
- Epilepsy. If there is an increase in epileptic attacks with **<Invented Name>**, the use of other contraceptive methods should be considered.
- Sydenham's chorea.
- Chronic inflammatory bowel diseases (Crohn's disease, ulcerative colitis).
- Hemolytic uremic syndrome.
- Uterine fibromyoma.
- Otosclerosis.
- Long immobilization (see also section 4.4.1).
- Obesity.
- Systemic lupus erythematosus.
- Women over 40 years of age.

4.4.3.2 Tumors

Breast
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 combined oral contraceptives. The excess risk gradually disappears during the course of the 10 years after cessation of combined oral contraceptive use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent combined oral contraceptive users is small in relation to the overall risk of breast cancer.

Cervix
Some epidemiological studies indicate that the long-term use of hormonal contraceptives by women infected with the Human Papilloma Virus (HPV) poses a risk factor for the development of cervix carcinoma. However, so far it is still not clear to what extent this result is affected by other factors (e.g. differences in the number of sexual partners or in the use of mechanical contraceptive methods) (see also section 4.4.4).

Liver
In rare cases, benign liver tumours have been reported in users of combined oral contraceptives. 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 combined oral contraceptives.

Studies have shown an increased risk of developing liver cell carcinomas in the long-term use of combined oral contraceptives; however, this tumor is extremely rare.

4.4.3.3 Other conditions

Hypertension

Hypertension has been reported when combined oral contraceptives were used, especially by older women and with long-term use. Studies have shown that the frequency of hypertension increases with the progestogen content. Women with medical history of hypertension-related diseases or certain kidney diseases should be advised to use other contraceptive methods (see sections 4.3, 4.4.1, 4.4.2).

Chloasma

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 combined oral contraceptives.

Hereditary angioedema

In women with hereditary angioedema, exogenous estrogen can cause or exacerbate symptoms of angioedema.

Irregular Bleedings

Breakthrough or spottings have been observed in users of combined oral contraceptives, especially in the first months of therapy. For this reason, an evaluation of these intermediate bleeding makes sense only after a treatment period of about three months. The type and dose of progestogen may therefor be significant. In case of persistent or recurrent bleeding irregularities occur after previously regular cycles, then non-hormonal causes should be considered and, as with any unusual vaginal bleeding, adequate diagnostic measures must be taken to rule out malignant disease and pregnancy. If both have been ruled out, **<Invented Name>** can continue to be taken or switched to another hormonal contraceptive. Bleeding between periods may be evidence of reduced contraceptive efficacy (see sections 4.2 and 4.5).

Some users may not have the withdrawal bleeding during the tablet-free interval. If **<Invented Name>** was not taken according to section 4.2.1 before the first missed withdrawal bleeding or the withdrawal bleeding fails in two consecutive cycles, pregnancy should be excluded before further intake.

After discontinuation of hormonal contraceptives, it may take some time to re-run a normal cycle.

4.4.3.4 Reduced efficacy

The contraceptive efficacy of **<Invented Name>** can be compromised

- if the person forgets to take the pill (see section 4.2.4).

- in cases of vomiting or diarrhea (see section 4.2.5),

- if certain other medications are being taken concomitantly (see section 4.5)

If combined oral contraceptives and St. John's wort (Hypericum perforatum) are used concomitantly, an additional non-hormonal contraceptive method is recommended (see section 4.5).

4.4.4 Medical examination/consultation

Prior the initiation or reinstitution of combined oral contraceptives a complete medical history (including family history) should be taken. 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 examinations should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that hormonal contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

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 Influence 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 active tablets in the COC pack, the placebo tablets must be discarded and the next COC pack should be started right away.

Long-term treatment

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

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).

Drugs that increase the gastrointestinal motility, e.g. metoclopramide, can reduce the serum concentration of <**Invented name**>.

Substances with variable effects on the clearance of COCs

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

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.
The following active substances can increase the serum concentration of the sexual steroids contained in **<Invented Name>**.

- Active substances that inhibit the sulphation of ethinylestradiol in the gastrointestinal wall, e.g. ascorbic acid or paracetamol.

- Atorvastatin (increase in AUC of ethinylestradiol by 20%),

- Active substances that inhibit liver microsomal enzymes, such as imidazole antimycotics (e.g. fluconazole), indinavir and troleandomycin.

The sexual steroids contained in <Invented Name> can affect the metabolization of other active substances

- By inhibiting liver microsomal enzymes resulting in increased serum concentrations of active substances such as diazepam (and a some other benzodiazepines), ciclosporine, theophylline and glucocorticoids.

- By inducing hepatic glucoronidation, resulting in decreased serum concentration e.g. of clofibrate, paracetamol, morphine, lorazepam (as well as some other benzodiazepines) and lamotrigine.

In-vitro studies have shown that dienogest in relevant concentrations does not inhibit cytochrome P-450 enzymes, so that no medication side-effects can be expected on that side.

The need for insulin or oral hypoglycemic agents may be altered as a result of the influence of glucose tolerance.

Side-effects with laboratory tests

The use of combined oral contraceptive 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> should not be used during pregnancy.

Pregnancy must be ruled out before starting to use the medication. If pregnancy occurs during use, the medication should be discontinued immediately.

Epidemiological studies indicate no increased risk of congenital anomalies in children born to women who used oral contraceptives prior to pregnancy. The majority of recent epidemiological studies also do not indicate a teratogenic effect, when taken inadvertently during early pregnancy. Such studies were not performed with **<Invented Name>**.

There are too limited data available about the use of **<Invented Name>** during pregnancy to allow conclusions in terms of negative effects of **<Invented Name>** on pregnancy and on the health of the fetus or newborn. So far, no relevant epidemiological data are available.

Animal studies have shown undesirable effects during gestation and lactation (see section 5.3). Based on these experimental results in animals, an undesirable hormonal effect of the active substances cannot be ruled out. General experiences with combination compounds for oral contraception during pregnancy, however, did not showed any evidence of adverse effects in humans.

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

<Invented Name> should not be used during the lactation period, since milk production can be reduced and small amounts of the active substances may be excreted in breast milk. If possible, non-hormonal contraception methods should be used until the child is fully weaned.

4.7 Effects on ability to drive and use machines

<Invented Name> has no effect on ability to drive and the ability to drive or operate machines.

4.8 Undesirable effects

Serious undesirable effects in the user, see section 4.4.

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 frequencies of adverse events with the use of <Invented Name> for oral contraception and for the treatment of moderate acne in clinical trials (N = 4.942) are summarized in the following table.

The frequency of possible side effects listed below are defined as:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

See the table

System organ class (MedDRA v.12.0)	**Common**	**Uncommon**	**Rare**	**Not Know**
Infections and infestations		Vaginitis / vulvovaginitis, vaginal candidiasis or signals vulvo-vaginal yeast infections	Salpingo-oophoritis, urinary tract infections, cystitis, mastitis, cervicitis, fungal infections called candidiasis, labial herpes, influenza, bronchitis, sinusitis, upper respiratory infections, viral infections	
Benign, malignant and unspecified neoplasms(including cysts and polyps)			Uterine leiomyoma, breast lipoma	
Blood and lymphatic system disorders			Anemia	
Immune system disorders			Hypersensitivity	
Endocrine disorders			Virilism	
Metabolism and nutrition disorders		Increased appetite	Anorexia	
Psychiatric disorders		Depressive mood	Depression, mental disorders, insomnia, sleep disturbances, aggressive reactions	Mood changes, reduced libido, increased libido
Nervous system disorders	Headaches	Migraines, dizziness	Ischemic stroke and cerebrovascular disorders, dystonia	
Eye disorders			Dry eye, eye irritation, oscillopsia, deterioration of vision	Contact lens intolerance
Ear and labyrinth disorders			sudden hearing loss, tinnitus, vertigo, hearing impairment	
Heart disorders			cardiovascular disorders, tachycardia [1]	
Vascular disorders		Hypotension, hypertension	Thrombophlebitis, VTE or ATE/pulmonary embolism, diastolic hypertension, orthostatic hypotension, flushing, varicose veins, venous disorders, veins pain	
Diseases of the respiratory tract, thoracic and mediastinal disorders			Asthma, hyperventilation	
Gastrointestinal		Abdominal pain [2],	Gastritis, Enteritis, Dyspepsia	

disorders		nausea, vomiting, diarrhea		
Skin and subcutaneous tissue disorders		Acne, alopecia, rash[3], pruritus[4]	allergic dermatitis, atopic dermatitis / eczema, eczema, psoriasis, hyperhidrosis, chloasma, skin discoloration / hyperpigmentation, seborrhea, dandruff, hirsutism, skin lesions, skin reactions, orange peel, skin nevus	Urticaria, erythema nodosum, erythema multiforme
Musculoskeletal and connective tissue disorders			Back pain, musculoskeletal complaints, myalgia, pain in the extremities	
Reproductive system and breast disorders	Breast pain[5]	irregular menstrual bleeding[6], metrorrhagia[7], breast enlargement[8], breast edema, dysmenorrhea, vaginal discharge, ovarian cysts, pelvic pain	Cervical dysplasia, cysts of the adnexa uteri pain of the adnexa uteri, breast cyst, fibrocystic breast disease, dyspareunia, galactorrhea, menstrual disorders	Breast gland secretion
General disorders and complaints administration		Tiredness [9]	Chest pain, peripheric edema, influenz-like diseases, inflammation, pyrexia, irritability	Fluid retention
Investigations		Weight changes[10]	Increase in blood triglycerides, hypercholesterolemia	
Congenital, familial and genetic disorders			Manifestation of asymptomatic accessory breast	

[1] Including increased heart rate
[2] Including the pain in the upper and lower abdomen, abdominal discomfort, bloating
[3] Includes rash maculares
[4] Including generalized pruritus
[5] Including breast symptoms and breast tenderness
[6] Including menorrhagia, hypomenorrhoe, oligomenorrhea and amenorrhea
[7] Consists of vaginal hemorrhage and metrorrhagia
[8] Including breast swelling / swelling
[9] Including asthenia and malaise
[10] Including weight gain, decrease and fluctuations

To a certain side effect to describe, respectively, the best-applicable concerned MedDRA terms (version 12.0) have been listed. Synonyms or related conditions are not listed, but should be considered. The following serious side effects were in women using COCs, reports, which are discussed in section 4.4:

• Venous thromboembolic diseases

• Arterial thromboembolic diseases

• Cerebrovascular events

• Hypertension

• Hypertriglyceridemia

• Modification of the glucose tolerance or loading influencing the peripheral insulin resistance

• Liver tumors (benign and malignant)

• Hepatic dysfunction

• Chloasma

• In women with hereditary angioedema to exogenous estrogens, the trigger or intensify symptoms of angioedema.

• Occurrence or worsening of illnesses, not clarified their relationship with the use of COCs is: jaundice and / or pruritus in connection with cholestasis; formation of gallstones; porphyria, systemic lupus erythematosus, haemolytic uraemic syndrome, Sydenham's chorea, herpes gestationis, otosclerosis related with hearing loss , Crohn's disease, ulcerative colitis, cervical cancer

The frequency of diagnosis of breast cancer is increased in users of oral contraceptives. Because breast cancer in women under 40 years rarely occurs, the number of additional diseases in comparison to the overall risk is small. A causal connection with the use of COCs is not known. For more information see section 4.3. and 4.4.

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 reactins after authorization 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

Symptoms of an overdose of combined oral contraceptives in adults and children can include: Nausea, vomit, breast tenderness, dizziness, stomach ache, sleepiness/fatigue; in women and girls vaginal bleeding can occur. There are no specific antidotes. Treatment is symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations

ATC code: G03AA

<Invented Name> is an effective antiandrogen compound for oral contraception, consisting of the estrogen ethinylestradiol and the progestogen dienogest.

The contraceptive effective of **<Invented Name>** is based on the combined interaction of different factors, where ovulation inhibition and changes in vaginal secretion are the most important.

The antiandrogenic effect of the combination of ethinylestradiol and dienogest is based, among other things, on the reduction of androgen concentration in the serum. In a multicentric study with **<Invented Name>**, an essential improvement in symptoms from mild to moderate acne, as well as

a favorable effect on seborrhea could be shown.

Ethinylestradiol

Ethinylestradiol is a powerful orally effective synthetic estrogen. As the naturally occurring estradiol, ethinylestradiol has a proliferative effect on the epithelia of the female genital organs. It stimulates the production of the cervical mucus, reducing its viscosity and increasing its fibrosity. Ethinylestradiol stimulates the growth of the lactiferous ducts and inhibits lactation. Ethinylestradiol stimulates extracellular fluid retention. Ethinylestradiol affects parameters of lipid and carbohydrate metabolism, hemostasis, rennin-angiotensin-aldosterone system and serum binding proteins.

Dienogest

Dienogest is a 19 nortestosteron derivate with 10 to 30 times lower in-vitro affinity to the progesterone receptor compared to other synthetic progestogens. In-vivo data in animals showed a strong progestogen effect and an antiandrogen effect. Dienogest in vivo has no significant androgenic, mineralocorticoids or glucocorticoid effect.

The ovulation-inhibiting dose of dienogest alone was defined with 1 mg/d.

5.2 Pharmacokinetic properties

- Ethinylestradiol

Absorption

Ethinylestradiol is rapidly and fully absorbed following oral administration. Maximum serum concentrations of about 67 pg/ml, are reached approximately 1.5 to 4 hours after intake of a **<Invented Name>** tablet.
During absorption and the first-pass metabolism in the liver, ethinylestradiol is extensively metabolized, resulting in a mean oral bioavailability of approximately 44%.

Distribution

Ethinylestradiol is pronounced (about 98 %) but is non-specifically bound to serum albumin and induces an increase in serum concentrations of sexual hormone binding globulin (SHBG). The absolute distribution of volume of ethinylestradiol is 2.8 to 8.6 l/kg.

Biotransformation

Ethinylestradiol is eliminated by presystemic conjugation in mucous membrane of the small intestine and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation; in that process different hydroxylated and methylated metabolites are formed, which are detectable as free metabolites or as a glucuronide sulphate conjugates in the serum. Ethinylestradiol is subjected to an enterohepatic circuit.

Elimination

The serum levels of ethinylestradiol decrease in two phases, characterized by half-life periods of about 1 hour and 10 – 20 hours.

Ethinylestradiol is not excreted in unchanged form. The metabolites are excreted in urine and the bile in a ratio of 4: 6.

- Dienogest

Absorption

Dienogest is rapidly and almost completely absorbed after oral administration. Maximum serum concentrations of 51 ng/ml after about 2.5 hours following a single intake of one **<Invented Name>** tablet. An absolute bioavailability of approximately 96% was detected in combination with ethinylestradiol.

Distribution

Dienogest is bound to the serum albumin and does not bind to SHBG or corticosteroid-binding globulin (CBG). Approximately 10% of the total serum drug concentration is present as free steroid. 90% is not specifically bound to albumin. The apparent distribution volume of dienogest is from 37 to 45 liters.

Biotransformation

Dienogest is mainly degraded by hydroxylation and by conjugation to endocrinologically extensively inactive metabolites. These metabolites are quickly eliminated from plasma, so that, besides the unchanged dienogest in human plasma, no essential metabolite was found. The total clearance (Cl/F) after a single dose is 3.6 l/h.

Elimination

The dienogest serum levels decrease with a half-life time of approximately 9 hours. Only negligible amounts of dienogest are renally excreted in unchanged form. After the oral administration of 0.1 mg of dienogest per kg of body weight, the ratio of renal to fecal excretion is 3.2. Within 6 days, approximately 86% of the administered dose is eliminated, where the majority, i.e. 42% is excreted in the first 24 hours through urine.

Steady state

The pharmacokinetics of dienogest is not influences by the SHBG level. In case of a daily intake, the serum drug levels increase approximately 1.5 times and after a 4-day administration, reach the steady state.

5.3 Preclinical safety data

The toxicity profile of ***Ethinylestradiol*** is well known.

Due to a marked species difference, the animal experimental findings with estrogens have only a limited predictive value for human use.

In laboratory animals, ethinylestradiol showed already at relatively low doses an embryolethal effect; malformations of the urogenital tract and feminization of male fetuses were observed.

Reproduction toxicity studies with ***Dienogest*** showed the typical progestogen effects, such as

increased pre- and post-implantation losses, lengthened gestation and increased neonatal mortality in the offsprings. After high doses of dienogest in late pregnancy and during lactation, the fertility of the offsprings was affected.

In preclinical data about toxicity gathered in conventional studies after repeated administration, genotoxicity and carcinogenity do not show any special risk for people, except for the information already presented in other sections of this SPC, and generally apply for the intake of oral contraception compounds.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core
Lactose monohydrate
Magnesium stearate
Maize starch
Povidone K-30

Film coating
Hypromellose 2910
Macrogol 400 (PEG)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30ºC
Keep the blister in the outer carton in order to protect from the light

6.5 Nature and contents of container

PVC/PVDC/Aluminum blister, pack sizes: 21 and 3x21 and 6x21 film-coated tablets.

The blister packs may come with a blister holder.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7.Marketing authorization holder

<[To be completed nationally]>

8. Marketing authorisation number(s)

<[To be completed nationally]>

9. Date of first authorisation/renewal of the authorisation

<[To be completed nationally]>