SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ditinell 0,060 mg/ 0,015 mg filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each yellow active tablet contains 0.060 mg of gestodene and 0.015 mg of ethinylestradiol.
The white placebo tablet does not contain active ingredients.

Excipients with known effect
The yellow active tablet contains 57.61 mg of lactose monohydrate and 0,042 mg of lecithin (soya).
The white tablet contains 70.897 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

<Invented name> yellow tablet is round, plain, and film-coated tablet of 5.5 mm diameter.
The white tablet (placebo) is round and biconvex tablet of 5.5 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

Posology

The tablets must be taken every day at about the same time, if necessary with a little liquid, in the order shown on the blister pack. Tablet taking is continuous. One tablet is to be taken daily for 28 consecutive days. Each subsequent pack is started the day after the last tablet of the previous pack. Withdrawal bleeding usually starts on day 2-3 after starting the placebo tablets (last row) and may not have finished before the next pack is started.

How to start <invented name>

- No preceding hormonal contraceptive use in the past month

Tablet-taking has to start on day 1 of the women's natural cycle (i.e. the first day of her menstrual bleeding).

- Changing from a 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 the 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 o transdermal patch has been used the woman should start using <invented name> preferably on the day of removal, but at the latest when the next application would have been due.

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

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

- Following first-trimester abortion

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

- Following delivery or second-trimester abortion

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

For breastfeeding women see section 4.6.

Management of missed tablets

Placebo tablets from the last (4^{th}) row of the blister can be disregarded. However, they should be discarded to avoid unintentionally prolonging the placebo tablet phase. The following advice only refers to **missed active tablets**:

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 taking any tablet, contraception 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 4 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:

- Day 1-7

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the

possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the placebo tablet phase, the higher the risk of a pregnancy.

- Day 8-14

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

- Day 15-24

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

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until the active tablets are used up. The 4 placebo tablets from the last row must be discarded. The next blister pack must be started right away. The user is unlikely to have a withdrawal bleed until the end of the active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.
2. The woman may also be advised to discontinue active tablet-taking from the current blister pack. She should then take placebo tablets from the last row for up to 4 days, including the days she missed tablets, and subsequently continue with the next blister pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the placebo tablet phase, the possibility of a pregnancy should be considered.

Advice in case of gastrointestinal 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 active tablet-taking, a new (replacement) tablet should be taken as soon as possible. The new tablet should be taken within 12 hours of the usual time of tablet-taking if possible. If more than 12 hours elapse, the advice concerning missed tablets, as given in section 4.2 “Management of missed tablets”, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another blister pack.

How to postpone a withdrawal bleed

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

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming placebo tablet phase by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

<u>Method of administration</u>

For oral use.

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following conditions.
Should any of the conditions appear for the first time during COC use, the use of the product must be stopped immediately.

- Presence or risk of venous thromboembolism (VTE)
    - Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE])
    - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
    - Major surgery with prolonged immobilisation (see section 4.4)
    - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)

- Presence or risk of arterial thromboembolism (ATE)
    - Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
    - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)
    - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
    - History of migraine with focal neurological symptoms.
    - A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
        - diabetes mellitus with vascular symptoms
        - severe hypertension
        - severe dyslipoproteinaemia
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding
- History of migraine with focal neurological symptoms
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Patients who are allergic to peanut or soya (lecithin)
- <invented name> is contraindicated for concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, medicinal products containing glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

4.4 Special warnings and precautions for use

Warnings

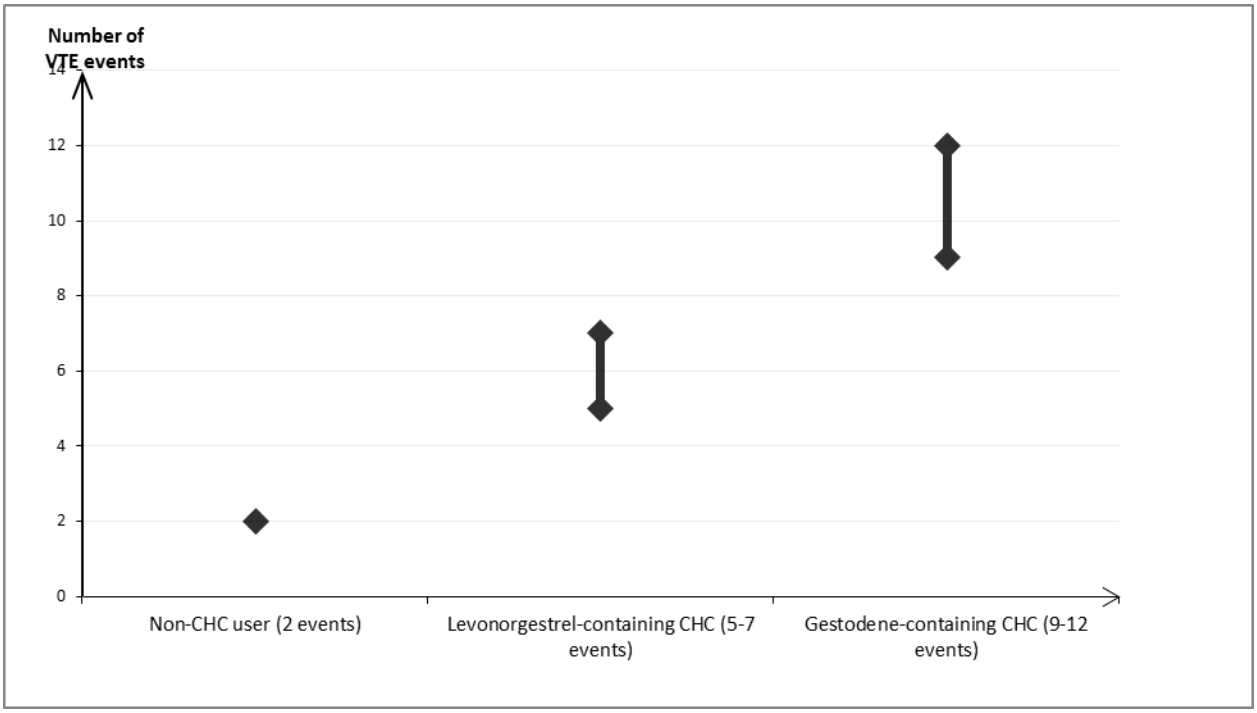
General
Women should be advised that COCs do not protect against HIV (AIDS) or other sexually transmitted infections (STI).

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. In case of suspected or confirmed VTE or ATE, CHC use should be discontinued. In case anti-coagulant therapy is started, adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

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 gestodene 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	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.

be a risk factor for VTE, particularly in women with other risk factors	
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.

Medical examination/consultation

Prior to the initiation or reinstitution of <invented name> a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contra-indications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of <invented name> compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

The woman should also be instructed to carefully read the user leaflet and to adhere 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 (AIDS) and other sexually transmitted infections**.**

Tumours

Cervical cancer
In some epidemiological studies an increased risk of cervical cancer has been reported in long term users of COCs, but it is still not clear to which this finding may be influenced by impacts of sexual behaviour and other factors, such as human papilloma virus (HPV).

Breast cancer
A meta-analysis of 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in woman 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 below 40 years of age, the excess number of breast cancer diagnoses in current and recent users of COC 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.

Liver tumours
Benign and malignant liver tumours have been reported in users of COCs. These tumours have, in isolated cases, lead to life threatening, intra-abdominal haemorrhage. A liver tumour must be taken into consideration as a differential diagnosis when severe pain occurs in the upper abdomen, if there is hepatomegaly, or of there are signs of intra-abdominal haemorrhage in women taking COCs.

Other conditions

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

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

Even though slight increases in blood pressure have been reported in many women taking COCs, clinically important increases in blood pressure are rare. If persistent clinical hypertension develops during

COC use, intake should be discontinued and the hypertension treated. Use of COCs may be resumed, if appropriate, when normotensive values are reached with antihypertensive therapy.

It has been reported that the following conditions may occur, or worsen both during pregnancy and during use of COCs, but the evidence of a relationship is inconclusive: Jaundice and/or pruritus in connection with cholestasis, development of gallstones; porphyria, systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; loss of hearing due to otosclerosis.

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

COCs may have an influence on peripheral insulin resistance and glucose tolerance. Therefore, diabetics should be closely monitored during COC use.

Worsening of endogenous depression, of epilepsy (see section 4.5 interactions), of Crohn's disease and of ulcerative colitis has been reported during COC use.

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Chloasma may occur, in particular in women with a medical history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to sunlight or ultraviolet radiation while taking COCs.

Reduced efficacy
The efficacy of oral contraceptives may be reduced in the case of missed tablets, severe diarrhoea or vomiting (see section 4.2), or concomitant use of other medicinal products (see section 4.5).

Reduced cycle control
With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

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

In some women withdrawal bleeding may not occur during the placebo tablet phase. If the COC has been taken according to the directions described in section 4.2, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

<u>Lactose</u>
Each yellow (active) tablet of this medicinal product contains 57.61 mg, each white (placebo) tablet contains 70.897 mg lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

<u>Soya (lecithin)</u>
The yellow (active) tablet contains 0,042 mg of lecithin (soya), therefore patients who are allergic to peanut or soya must not take this medicine.

Sodium
The white (placebo) tablet contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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.

Pharmacodynamic interactions
During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see section 4.3).
Therefore, <invented name>-users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these combination drug regimens. <invented name> can be restarted 2 weeks following completion of treatment with these combination drug regimens.

- Effects of other medicinal products on <Invented name>

Interactions can occur with medicines 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 this medicine, enzyme induction may be sustained for about 4 weeks.

Short-term treatment
Women on treatment with enzyme-inducing medicines 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 therapy with this medicine and for 28 days after its discontinuation.

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

The following interactions have been reported in the literature.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.:
Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (Hypericum perforatum).

Substances with variable effects on the clearance of COCs:
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.

Substances decreasing the clearance of COCs (enzyme inhibitors):
The clinical relevance of potential interactions with enzyme inhibitors remains unknown. Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the estrogen or the progestin or both.

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

- Effects of <Invented name> on other medicinal products

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

Clinical data suggests that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

- 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 blood carbohydrate metabolism, and parameters of coagulation and fibrinolysis. Changes generally remain within the normal range.

4.6 Fertility, pregnancy and lactation

Pregnancy

<invented name> is not indicated in pregnancy.
If the woman becomes pregnant while using <invented name> tablets, further intake must be stopped immediately.

However, most epidemiological studies have revealed neither an increased risk of birth defects in children born to women taking contraceptive pills before pregnancy, nor any teratogenic effects at unintentional intake of contraceptive pills in early pregnancy.

The increased risk of VTE during the postpartum period should be considered when re-starting <invented name> (see section 4.2 and 4.4).

Breastfeeding
Lactation may be influenced by contraceptive pills since they may reduce the amount of breast milk and change its composition. Thus, the use of combined oral contraceptives should generally not be

recommended until the breast-feeding mother has weaned her child off breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted in breast milk. These amounts may affect the infant.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following undesirable effects have been reported in users of COCs:

For serious undesirable effects in COC users see section 4.4.

The occurrence of amenorrhea was reported in 15% of women during clinical trial, see section 4.4.

Some most frequently (greater than 10 %) reported adverse events during phase III studies and post-marketing surveillances in women using gestodene and ethinylestradiol are headache, including migraines, breakthrough bleeding/spotting.

Other adverse events have been reported in women taking COC:

	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** (frequency cannot be estimated from the available data)
Infections and infestations	Vaginitis, including candidiasis				
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Hepatocellular carcinoma and benign hepatic tumors (e.g. focal nodular hyperplasia, hepatic adenoma)	

	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** (frequency cannot be estimated from the available data)
Immune system disorders			Anaphylactic/ anaphylactoid reactions, including very rare cases of urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms.	Exacerbation of systemic lupus erythematosus	Exacerbation of symptoms of hereditary and acquired angioedema
Metabolism and nutrition disorders		Changes in appetite (increase or decrease)	Glucose intolerance	Exacerbation of porphyria	
Psychiatric disorders	Mood changes, including depression, changes in libido				
Nervous system disorders	Nervousness, dizziness			Exacerbation of chorea	
Eye disorders			Intolerance to contact lenses	Optic neuritis, retinal vascular thrombosis	
Vascular disorders		Increase in blood pressure	VTE or ATE		
Gastrointestinal disorders	Nausea, vomiting, abdominal pain	Abdominal cramps, bloating		Pancreatitis	
Hepatobiliary disorders			Cholestatic jaundice	Biliary lithiasis and cholestasis[1], hepatic and hepatobiliary disorders (e.g. hepatitis, hepatic function abnormal)	

	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** (frequency cannot be estimated from the available data)
Skin and subcutaneous tissue disorders	Acne	Rash, chloasma (melasma), which may persist, hirsutism, alopecia	Erythema nodosum	Erythema multiforme	
Renal and urinary disorders				Haemolytic uremic syndrome	
Reproductive system and breast disorders	Breast pain, tenderness, enlargement, secretion, dysmenorrhea, change in menstrual flow, change in cervical ectroption and secretion.				
General disorders and administration site conditions	Fluid retention/oedema				
Investigations	Changes in weight (increase or decrease)	Changes in serum lipid levels, including hypertriglyceridemia			

[1]COCs may worsen existing biliary lithiasis and cholestasis

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, which are discussed in section 4.4 Special warnings and precautions for use:

- Hypertension;
- Liver tumours;
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, migraine, uterine myoma, porphyria, systemic lupus

erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic 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.
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired 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.

Interactions
Breakthrough bleeding and/or contraceptive failure may result from interactions of other medicines (enzyme inducers) with oral contraceptives (see section 4.5).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There have been no reports of serious adverse effects from overdose. Symptoms that may be caused by overdose are nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and the treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormonal contraceptives for systemic use, progestogens and estrogens, fixed combinations, ATC code: G03AA10

The overall Pearl index (pregnancies due to method failure + pregnancies due to patient failure) for Gestodene / Ethinylestradiol 60/15 µg is 0.24 (95%CI 0.04-0.57).
The contraceptive effect of COCs is based on the interaction of various factors. The most important of these factors are the inhibition of ovulation and changes in the endometrium.

5.2 Pharmacokinetic properties

Gestodene:

Absorption
After oral administration gestodene is rapidly and completely absorbed. The absolute bioavailability is about 100%. After oral intake of a single 60 µg gestodene dose, peak plasma concentrations of 2 ng/mL are reached in about 60 minutes. The plasma concentrations are strongly dependent on the SHBG concentrations.

Distribution

Gestodene has an apparent volume of distribution of 1.4 L/kg following a single 60 µg dose. It is 30% bound to plasma albumin and 50-70% bound to SHBG.

Biotransformation
Gestodene is extensively metabolised by the steroid metabolic pathway. The metabolic clearance is about 0.8 mL/min/kg following a single 60 µg dose. The non-active metabolites formed are excreted in urine (60%) and faeces (40%).

Elimination
The apparent elimination half-life of gestodene is about 13 hours. The half-life is prolonged to 20 hours after concomitant administration with ethinylestradiol.

Linearity/non-linearity
After multiple dosing concomitantly with ethinylestradiol the plasma concentration increases approximately by a factor of 2-4.

Ethinylestradiol:

Absorption
Ethinylestradiol is rapidly and completely absorbed after oral ingestion. After administration of 15 µg, peak plasma concentrations of 30 pg/mL are reached after 1-1.5 hours. Ethinylestradiol undergoes an extensive first pass effect, which displays great interindividual variation. The absolute bioavailability is approximately 45%.

Distribution
Ethinylestradiol has an apparent volume of distribution of 15 L/kg and binding to plasma proteins is approximately 98%. Ethinylestradiol induces the hepatic synthesis of sex-hormone binding globulins (SHBG) and corticoid-binding globulins (CBG). During treatment with 15 µg ethinylestradiol the plasma concentration of SHBG increases from 86 to about 200 nmol/L.

Biotransformation
Ethinylestradiol is metabolised completely (metabolic plasma clearance approximately 10mL/min/kg). The metabolites formed are excreted in the urine (40%) and faeces (60%).

Elimination
The elimination half-life of ethinylestradiol is approximately 15 hours. Ethinylestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinylestradiol are excreted at a urinary to biliary ratio of 4:6.

Linearity/non-linearity
Steady state conditions are reached during the second half of the treatment cycle and serum levels of ethinylestradiol accumulate by a factor of about 1.4 to 2.1.

5.3 Preclinical safety data

Gestodene and ethinylestradiol are not genotoxic. Carcinogenicity studies with ethinylestradiol alone or in combination with various progestogens do not indicate any particular carcinogenic hazard to women when used as indicated for contraception. However, it should be noted that sex hormones can advance the growth of certain hormone-dependent tissues and tumours.

Reproductive toxicity studies on fertility, development of the fetus or reproductive ability with ethinylestradiol alone or in combination with progestogens revealed no undesirable effects for humans when used as recommended.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active tablets (Yellow tablets):

Tablet core:
Lactose monohydrate
Microcrystalline cellulose (E460)
Polacrilin potassium
Magnesium stearate (E572)

Coating:
Polyvinyl alcohol
Titanium dioxide (E-171)
Lecithin (soya) (E322)
Talc
Iron Oxide Yellow (E-172)
Xanthan gum (E415)

Placebo tablets (white tablets):

Lactose monohydrate
Povidone K25 (E1201)
Sodium starch glycolate (type A)
Silica colloidal anhydrous (E551)
Aluminium oxide, anhydrous
Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep blister in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Clear to slightly opaque transparent PVC/PVDC-Al blister.

Pack sizes:
1 × 28 (24 active plus 4 placebo) film coated tablets
3 × 28 (24 active plus 4 placebo) film coated tablets
6 × 28 (24 active plus 4 placebo) film coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

Egis Pharmaceuticals PLC.
Keresztúri út 30-38
1106 Budapest
Hongrije

8. MARKETING AUTHORISATION NUMBERS

RVG 114056

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 22 augustus 2014

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.3, 4.4 en 4.5: 20 oktober 2022.