## 1. NAME OF THE MEDICINAL PRODUCT

Microgynon 30 Tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

21 hormone-containing beige coated tablets:
Each coated tablet contains 0.15mg levonorgestrel and 0.03 mg ethinylestradiol.

For a full list of excipients, see section “List of excipients”.

## 3. PHARMACEUTICAL FORM

Coated tablet

## 4. CLINICAL PARTICULARS

### 4.1 Indications

Oral Contraception.

### 4.2 Dosage and method of administration

#### 4.2.1 Method of administration

Oral use

#### 4.2.2 Dosage regimen

*How to take Microgynon 30*

Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year. The failure rate may increase when pills are missed or taken incorrectly.

Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. 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 coated tablet and may not have finished before the next pack is started.

*How to start Microgynon 30*

● *No preceding hormonal contraceptive use (in the past month)*

Tablet-taking has to start on day 1 of the woman’s natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2–5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

● *Changing from a combined hormonal contraceptive (combined oral contraceptive/COC), vaginal ring, or transdermal patch*

The woman should start with Microgynon 30 preferably on the day after the last hormone-containing tablet of her previous COC, but at the latest on the day following the usual tablet-free or hormone-free tablet interval of her previous COC. In case a vaginal ring or transdermal

patch has been used, the woman should start using Microgynon preferably on the day of removal of the last ring or patch of a cycle pack, but at the latest when the next application would have been due.

● *Changing from a progestogen-only-method (minipill, injection, implant)*

The woman may switch any day from the minipill (from an implant 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 does not need additional contraceptive measures.

● *Following delivery or second-trimester abortion*

For breastfeeding women see section on “Pregnancy and Lactation”.

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 of tablet-taking. 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.

*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 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 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 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 this is not the case, or if she 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 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, the woman should be advised to follow the first of these two options and to 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. The next pack must be started as soon as the current 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 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 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, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3-4 hours after tablet-taking, the advice concerning missed tablets, as given in section “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) needed from another pack.

*How to shift periods or how to delay a period*

To delay a period the woman should continue with another pack of Microgynon 30 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 Microgynon 30 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 second pack (just as when delaying a period).

### 4.2.3 Additional information on special populations

#### 4.2.3.1 Pediatric Patients

Microgynon 30 is only indicated after menarche.

#### 4.2.3.2 Geriatric patients

Not applicable. Microgynon 30 is not indicated after menopause.

#### 4.2.3.3 Patients with hepatic impairment

Microgynon 30 is contraindicated in women with severe hepatic diseases. See also section "Contraindications".

#### 4.2.3.4 Patients with renal impairment

Microgynon 30 has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

### 4.3 Contraindications

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

- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident.
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- A high risk of venous or arterial thrombosis (see section "Special Warnings and Precautions for Use").
- Severe hepatic disease as long as liver function values have not returned to normal.

- Use of direct –acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir,or dasabuvir, and combinations of these (See "Interaction with other medicinal products and other forms of interaction")

- 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.
- Known or suspected pregnancy.
- Hypersensitivity to the active substances or to any of the excipients.
- Jaundice or persistent itching during a previous pregnancy

- Sickle cell anemia
- Disturbances of lipometabolism
- History of herpes of pregnancy
- Otosclerosis with deterioration during pregnancy

**4.4 Special Warnings And Precautions For Use**

***Warnings***

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.

*Circulatory Disorders*

Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents. These events occur rarely.

The risk of VTE is highest during the first year of use. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

Overall the risk for venous thromboembolism (VTE) in users of low estrogen dose (< 50 µg ethinylestradiol) COCs is two to threefold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

VTE may be life-threatening or may have a fatal outcome (in 1-2 % of the cases).

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users.

Symptoms of deep venous thrombosis (DVT) can include: unilateral swelling of the leg 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 discolored 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 bring up blood; sharp chest pain which may increase with deep breathing; sense of anxiety; 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).

An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion or myocardial infarction (MI). 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 confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discolouration of an extremity; acute abdomen.

Symptoms of 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; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

Arterial thromboembolic events may be life-threatening or may have a fatal outcome.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. A COC should not be prescribed in case of a negative risk benefit assessment (see section “Contraindications”).

The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:
● age
● obesity (body mass index over 30 kg/$m^2$)
● a positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any COC use
● 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 to resume until two weeks after complete remobilization.
● smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
● dyslipoproteinemia;
● hypertension;
● migraine;
● valvular heart disease;
● atrial fibrillation;

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

The increased risk of thromboembolism in the puerperium must be considered (for information, see section “Pregnancy and Lactation”).

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

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.

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 that associated with low-dose COCs (<0.05 mg ethinylestradiol).

*Tumours*

The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g., cervical screening and sexual behaviour including 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 hemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.

Malignancies may be life-threatening or may have a fatal outcome.

*Other conditions*

Women with hypertriglyceridemia, 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. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or

pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of 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 low-dose COCs (containing < 0.05 mg ethinylestradiol). 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.

*Medical examination/consultation*

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the contraindications (see Section "Contraindications") and warnings (see Section "Special Warnings And Precautions For Use"), and should be repeated at least annually during the use of COCs. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

*Reduced efficacy*

The efficacy of COCs may be reduced in the event of missed tablets (see Section "Management of missed tablets"), gastro-intestinal disturbances (see section "Advice in case of gastro-intestinal disturbances") during tablet taking or concomitant medication (see section "Interactions with other medicinal products and other forms of interaction").

*Reduced cycle control*

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

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

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions described in section “Dosage and Administration”, 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**

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

***Effects of other medicinal products on Microgynon***

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. There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical studies in women demonstrate no evidence of an interaction between COCs and non-enzyme inducing antibiotics. Rifampicin and Griseofulvin are two enzyme inducing antimicrobials that are known to reduce the efficacy of COC.

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.

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. The barrier method should be used during the time of concomitant drug administration and for 28 days after their 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.

*Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.:*

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John’s wort.

*Substances with variable effects on the clearance of COCs, e.g.:*

When co-administered with COCs, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.

*Substances decreasing the clearance of COCs (enzyme inhibitors):*

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the estrogen or the progestin or both.

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

***Effects of COCs on other medicinal products***

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).
*In vitro*, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical studies, administration of a hormonal contraceptive containing ethinylestradiol did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g. midazolam) while plasma concentrations of CYP1A2 substrates can increase weakly (e.g. theophylline) or moderately (e.g. melatonin and tizanidine).

*Pharmacodynamic interactions*
Co-administration of ethinylestradiol-containing medicinal products with direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these has been shown to be associated with increases in ALT levels to greater than 20 times the upper limit of normal in healthy female subjects and HCV infected women (see 'Contraindications')

**Other forms of interactions**

- *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 generally remain within the normal laboratory range.

## 4.6 Pregnancy and lactation

### 4.6.1 Pregnancy

Microgynon 30 is not indicated during pregnancy. If pregnancy occurs during treatment with Microgynon 30, further intake must be stopped. However, extensive 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.

### 4.6.2 Lactation

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.

### 4.7 Effects on ability to drive or use machines

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

### 4.8 Undesirable Effects

### 4.8.1 Summary of the safety profile

The most commonly reported adverse reactions with Microgynon are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. They occur in ≥ 1 % of users.
Serious adverse reactions are arterial and venous thromboembolism.

### 4.8.2 Tabulated list of adverse reactions

Side effects that have been reported in users of COCs but for which the association has been neither confirmed nor refuted are*:

| **System Organ Class (MedDRA)** | **Common (≥1/100 to < 1/10)** | **Uncommon (≥1/1000 and <1/100)** | **Rare (>1/10000 to < 1/1000)** |
|---|---|---|---|
| Eye disorders | | | Contact lens intolerance |
| Gastrointestinal disorders | Nausea<br>Abdominal pain | Vomiting<br>Diarrhea | |
| Immune system disorders | | | Hypersensitivity |
| Investigations | Weight increased | | Weight decreased |
| Metabolism and nutrition disorders | | Fluid retention | |
| Nervous system disorders | Headache | Migraine | |
| Psychiatric disorders | Depressed mood<br>Mood altered | Libido decreased | Libido increased |
| Reproductive system and breast disorders | Breast pain<br>Breast tenderness | Breast hypertrophy | Vaginal discharge<br>Breast discharge |
| Skin and subcutaneous tissue disorders | | Rash<br>Urticaria | Erythema nodosum<br>Erythema multiforme |
| Vascular disorders | | | Venous and arterial thromboembolic |

| | | | |
|---|---|---|---|
| | | | events** |

*The most appropriate MedDRA term (version 12.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.
**
- Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives.
- 'Venous and arterial thromboembolic events' summarizes the following Medical Entities: Peripheral deep venous occlusion, thrombosis and embolism/Pulmonary vascular occlusion, thrombosis, embolism and infarction/Myocardial infarction/Cerebral infarction and stroke not specified as hemorrhagic

### 4.8.3 Description of selected adverse reactions

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of combined oral contraceptives are listed below (see also sections "Contraindications", "Special warnings and precautions for use"):

*Tumors*
• 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.
• Liver tumors (benign and malignant)

*Other conditions*
• Women with hypertriglyceridemia (increased risk of pancreatitis when using COCs)
• Hypertension
• Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss
• In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema
• Liver function disturbances
• Changes in glucose tolerance or effect on peripheral insulin resistance
• Crohn's disease, ulcerative colitis.
• Chloasma

*Interactions*
Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with oral contraceptives (see section 'Interaction with other medicinal products and other forms of interaction').

### 4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea, vomiting and withdrawal bleeding. The last may even occur in girls before their menarche, if they have accidentally taken the medicinal product.There are no antidotes and further treatment should be symptomatic.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC): Progestogens and estrogens, fixed combinations
ATC Code: G03AA

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

Post Authorization Safety Studies (PASS) have shown that the frequency of VTE diagnosis ranges between 7-10 per 10,000 woman years in low estrogen dose (< 50 µg ethinylestradiol) COC users. The most recent data suggest that the frequency of VTE diagnosis is approximately 4 per 10,000 woman years in non-pregnant non-COC users, and ranges between 20 to 30 per 10,000 pregnant women or postpartum.

### 5.2 Pharmacokinetic properties

***Levonorgestrel***

*Absorption*

Orally administered levonorgestrel is rapidly and completely absorbed. Peak serum concentrations of about 3 - 4 ng/ml are reached at about 1 hour after single ingestion. Levonorgestrel is almost completely bioavailable after oral administration.

*Distribution*

Levonorgestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1.3 % of the total serum drug concentrations are present as free steroid, approximately 64 % are specifically bound to SHBG and about 35 % are non-specifically bound to albumin. The ethinylestradiol-induced increase in SHBG influences the proportion of levonorgestrel bound to 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 levonorgestrel is about 184 l after single administration.

*Metabolism*

Levonorgestrel is extensively metabolized. The major metabolites in plasma are the unconjugated and conjugated forms of 3α, 5β-tetrahydrolevonorgestrel. Based on *in vitro* and *in vivo* studies, CYP3A4 is the main enzyme involved in the metabolism of levonorgestrel. The clearance rate from serum is approximately 1.3 - 1.6 ml/min/kg.

*Elimination*

Levonorgestrel serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of approximately 20 – 23 hours. Levonorgestrel is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1:1. The half-life of metabolite excretion is about 1 day.

*Steady-state conditions*

Following daily ingestion drug serum levels increase about three to four fold reaching steady-state conditions during the second half of a treatment cycle. Levonorgestrel pharmacokinetics are influenced by SHBG levels, which are increased about 1.7 fold after daily oral administration of Microgynon. This effect leads to a reduction of the clearance rate to about 0.7 ml/min/kg at steady-state.

***Ethinylestradiol***

*Absorption*

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 95 pg/ml are reached within 1 – 2 hours. During absorption and first-liver passage, ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of about 45% with a large interindividual variation of about 20-65%.

*Distribution*

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

*Metabolism*

Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized 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 glucuronides and sulfate. The clearance rate was reported to be 2.3 –7 ml/min/kg.

*Elimination*

Ethinylestradiol serum levels decrease in two disposition phases characterized by half-lives of about 1 hour and 10 – 20 hours, respectively. Unchanged drug is not excreted, ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion 1 day.

*Steady-state conditions*

Ethinylestradiol serum concentrations increase slightly after daily oral administration of Microgynon 30. The maximum concentrations are about 114 pg/ml at the end of a treatment cycle. According to the variable half-life of the terminal disposition phase from serum and the daily ingestion, steady-state serum levels of ethinylestradiol will be reached after about one week.

### 5.3 Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

calcium carbonate
ferric oxide pigment yellow
glycerol 85%
lactose monohydrate
macrogol 6000
magnesium stearate
maize starch
montanglycol wax
povidone 25
povidone 700 000
sucrose
talc
titanium dioxide

### 6.2 Incompatibilities

None

### 6.3 Shelf life

Refer to carton.

### 6.4 Storage Conditions

Store below 30°C. Store all drugs properly and keep them out of reach of children.

### 6.5 Presentation

Calendar pack containing 21 tablets

**Manufactured by**
Bayer Weimar GmbH und Co. KGD-99427 Weimar,
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Germany

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If you would like to report a side effect for any Bayer Pharmaceutical or Consumer Health product, you can do it easily using our online reporting portal: https://safetrack-public.bayer.com/ or scan the QR code available below. Please also remember to seek medical advice directly from your doctor or pharmacist.

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