Information for Healthcare Professionals

1. NAME OF THE MEDICINAL PRODUCT

Microgynon Fe 150 micrograms / 30 micrograms coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One coated tablet contains 150 µg levonorgestrel and 30 µg ethinylestradiol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet

21 active tablets: beige-coloured, round, convex and coated tablet.
7 inactive tablets: brown, round, convex and coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception

When deciding to prescribe Microgynon Fe, the current, individual risk factors of individual women, particularly with regard to venous thromboembolism (VTE), should be considered. Also, the risk of VTE with Microgynon Fe use should be compared with that of other combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Method of administration
For oral use

Posology
The tablets must be taken at approximately the same time each day, if required with some liquid, in the sequence stated on the blister. The tablets are taken continuously. 1 tablet must be taken daily for 28 consecutive days. Tablet-taking from the next pack is started after the last tablet from the previous pack has been taken. Withdrawal bleeding generally starts 2 to 3 days after starting to take the placebo tablets. It may persist when tablet-taking from the next pack has been commenced.

Starting to take Microgynon Fe

No preceding use of hormonal contraceptives [within the last month]
Tablet-taking should commence on day 1 of the natural cycle (i.e. on the first day of menstrual bleeding). If commenced between days 2 and 5, an additional contraceptive method is recommended for the first 7 days of the first treatment cycle.

Switching from another combined hormonal contraceptive (COC, vaginal ring, transdermal patch)
The user should preferably start taking Microgynon Fe on the day after taking the last active tablet of her previous combined product (or after removal of the ring or patch), but by no later than the day after the usual tablet-free (ring-free, patch-free) interval, or on the day after taking the last inactive tablet of the previous combined product.

Switching from a progestogen-only product (pill, injection, implant) or an intrauterine system (IUS)
In women previously taking the minipill, the switch can be made on any day of their choice (the switch from an implant or intrauterine system must take place on the day of its removal; the switch from an injectable must take place at the time when the next injection would be due). However, in all cases, an additional contraceptive method is required during the first 7 days of tablet-taking.

Following a first-trimester abortion
Tablet-taking can commence immediately. In this case, no additional contraceptive measures are required.

Following childbirth or a second-trimester abortion
For use during breast-feeding, see section 4.6.
Tablet-taking should commence on days 21 to 28 following childbirth or after a second-trimester abortion. If started any later, a barrier method must additionally be used during the first 7 days of tablet-taking. However, if sexual intercourse has already taken place, pregnancy must be excluded before the tablets are started, or the woman must wait for her first menstrual period.

Management of missed tablets
Microgynon Fe contains a very low dosage of the two hormones and the window of contraceptive efficacy is consequently very small if a tablet has been missed.

If the tablet is taken **within 12 hours** after the usual dosing time, contraceptive protection is not impaired. In this case, the forgotten tablet must be taken immediately. All subsequent tablets must then be taken at the usual time.

If the dosing time has been exceeded by **more than 12 hours**, contraceptive protection may be reduced. If tablets have been missed, 2 points should basically be remembered:

1. Active tablet-taking must never be discontinued for more than 7 days.
2. To achieve adequate suppression of the hypothalamic-pituitary-ovarian system, 7 days of uninterrupted active tablet-taking is required.

Accordingly, the following recommendations can be given for daily practice:

Week 1
The user should take the last missed tablet as soon as she realises she has forgotten it, even if this means taking two tablets at the same time. Subsequent tablets should then be taken at the usual time. However, a barrier method, for instance a condom, should additionally be used for the next 7 days. If sexual intercourse has taken place during the previous 7 days, the possibility of pregnancy should be considered. The more tablets have been forgotten and the closer the regular inactive tablet interval, the greater the risk of pregnancy.

Week 2
The user should take the last missed tablet as soon as she realises she has forgotten it, even if this means having to take two tablets at the same time. Subsequent tablets should then be taken at the usual time. Provided that the user has been taking her tablets correctly on the 7 days prior to the first forgotten tablet, there is no need to use additional contraceptive measures. If this has not been the case or if more than 1 tablet has been forgotten, the use of additional contraceptive measures for 7 days should be recommended.

Week 3
Due to the imminent 7-day inactive tablet interval, full contraceptive protection is no longer assured. However, a reduction in the contraceptive effect can be prevented by adjusting the dosing schedule. Thus, if either of the following courses of action is taken, there is no need for additional contraceptive measures, provided that the user has been taking her tablets correctly on the 7 days prior to the first forgotten tablet. If this has not been the case, the user should follow the course of action described under point 1 and also use additional contraceptive measures for the next 7 days.

1. The user should take the last forgotten active tablet as quickly as possible, even if this means taking two tablets at the same time. The remaining tablets should then be taken at the usual time. Tablet-taking from the next blister should be commenced immediately upon completion of the current pack, i.e. there is no inactive tablet interval between the two packs. The user is unlikely to experience withdrawal bleeding before finishing the second pack. However, spotting or breakthrough bleeding may occur while she is still taking her tablets.

2. It is also possible to stop taking the tablets from the opened blister. The user must then start taking the inactive tablets from the current blister and observe an inactive tablet interval of 7 days (including the days when she has forgotten the tablets) and then continue with a new pack.

If the user has missed several tablets and no subsequent withdrawal bleeding has occurred in the first normal inactive tablet phase, the possibility of pregnancy must be considered.

<u>What to do in the event of gastrointestinal disorders</u>
In the event of severe gastrointestinal disorders, the active substances may not be completely absorbed and additional contraceptive measures should be used.

If vomiting or severe diarrhoea occurs within the first 3–4 hours after taking a tablet, the same instructions for use apply as for missed tablets. If the user does not wish to deviate from her dosing schedule, she must take the replacement tablet from another blister.

<u>Postponing the timing of periods and changing the day of the week when periods start</u>
To postpone menstruation, the user should leave out the inactive tablets and immediately start taking tablets from the next pack of Microgynon Fe. The period can be delayed for as long as she desires, but until no later than the end of the second pack. During this time, breakthrough bleeding or spotting may occur. After the usual inactive tablet-taking interval, the user can continue to take Microgynon Fe as normal.

To postpone the start of menstruation to another day of the week, the next inactive tablet interval can be shortened by the desired number of days. The shorter the inactive tablet-taking interval, the greater the likelihood that withdrawal bleeding will be absent and that breakthrough bleeding or spotting will occur while tablets are taken from the next pack (exactly as with postponement of menstruation).

4.3 Contraindications

Combined oral contraceptives (COCs) must not be used in the presence of any of the following conditions. If any of these conditions occurs for the first time during COC use, the medicinal product must be discontinued immediately.

- Presence or risk of venous thromboembolism (VTE)
  - venous thromboembolism – existing VTE (including during therapy with anticoagulants) or history of VTE (e.g. deep vein thrombosis [DVT] or pulmonary embolism [PE])
  - known hereditary or acquired predisposition for venous thromboembolism, e.g. APC resistance (including Factor V Leiden), antithrombin III deficiency, protein C deficiency or protein S deficiency
  - major surgery with prolonged immobilisation (see section 4.4)
  - high risk of venous thromboembolism due to several risk factors (see section 4.4)
- Presence or risk of arterial thromboembolism (VTE)
  - arterial thromboembolism – existing ATE, history of ATE (e.g. myocardial infarction) or disease at the prodromal stage (e.g. angina pectoris)
  - cerebrovascular disease – existing stroke, history of stroke or prodromal disease (e.g. history of transient ischaemic attack [TIA])
  - known hereditary or acquired predisposition for arterial thromboembolism, e.g. hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant)
  - history of migraine with focal neurological symptoms
  - high risk of arterial thromboembolism due to several risk factors (see section 4.4) or a serious risk factor, such as:
    - diabetes mellitus with vascular damage
    - severe hypertension
    - severe dyslipoproteinaemia
- Existing or previous pancreatitis, if accompanied by severe hypertriglyceridaemia
- Existing or previous severe hepatic disease, until liver function values have returned to normal
- Existing or previous liver tumours (benign or malignant)
- Known or suspected sex hormone-dependent malignant tumours (e.g. of the genital organs or breast)
- Undiagnosed vaginal bleeding
- Amenorrhoea of unknown cause
- Hypersensitivity to the active substances levonorgestrel and ethinylestradiol or to any of the excipients listed in section 6.1.

Microgynon Fe is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, and medicinal products containing glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

4.4 Special warnings and precautions for use

Warnings

The suitability of Microgynon Fe should be discussed with the woman if any of the following disorders or risk factors is present.

If any of these disorders or risk factors deteriorates or appears for the first time, the user should be advised to contact her doctor to decide whether the use of Microgynon Fe should be terminated.

Risk of venous thromboembolism (VTE)

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with non-use. **The decision to use Microgynon Fe should be taken only after discussion with the woman, during which it should be ensured that she understands the following:**

- **the risk of VTE with Microgynon Fe use,**
- **how her existing, individual risk factors influence this risk,**
- **and that her risk of VTE is highest during her very first year of use.**

There are also indications that the risk is increased when CHC use is resumed after an interval of 4 weeks or more.

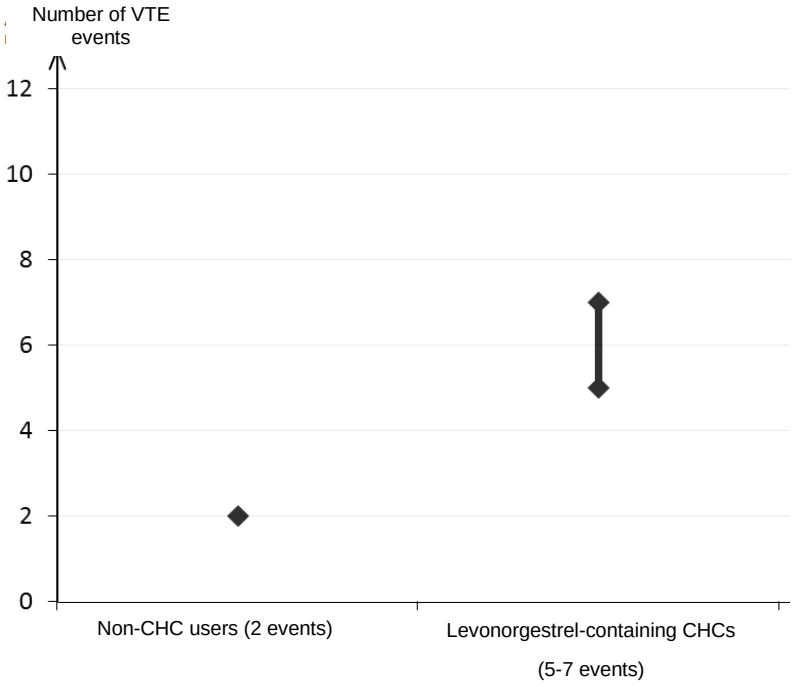
Approximately 2 out of 10,000 women not using a CHC and who are not pregnant will suffer a VTE during the course of a year. However, the risk may be significantly higher in individual women, depending on their underlying risk factors (see below).

Approximately 6[1] out of 10,000 women using a levonorgestrel-containing CHC will suffer a VTE during the course of a year.

The number of VTEs per year with low-dose CHCs is lower than the expected number during pregnancy or in the postpartum period.

VTEs are fatal in 1-2% of cases.

Annual number of VTE events per 10,000 women



In CHC users, there have been extremely rare reports of thrombosis in other blood vessels, e.g. in veins and arteries of the liver, mesentery, kidneys, brain or retina.

[1] Midpoint of range of 5-7 per 10,000 women-years, based on a relative risk for levonorgestrel-containing CHCs versus non-use of approximately 2.3 to 3.6

Risk factors for VTE

The risk of venous thromboembolic complications in CHC users can increase significantly if the user has additional risk factors; especially if several risk factors are present (see Table).

Microgynon Fe is contraindicated if a woman has several concomitant risk factors exposing her overall to a 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 overall risk of VTE must be considered. If the benefit/risk ratio is deemed to be unfavourable, no CHCs may be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	**Note**
Obesity (body mass index over 30 kg/m²)	The risk increases significantly with increasing BMI. Particularly important if other risk factors are present.
Prolonged immobilisation, major surgery, any leg or hip surgery, neurosurgery or severe trauma Note: Temporary immobilisation, including air travel > 4 hours, can also be a risk factor for VTE, especially in women with other risk factors.	In these cases, it is advisable to stop using the tablet (at least four weeks ahead of scheduled surgery) and not to resume it for at least two weeks after complete mobilisation. Another method of contraception should be used to prevent an unwanted pregnancy. Antithrombotic therapy must be considered if Microgynon Fe has not been discontinued in advance.
Family predisposition (any venous thromboembolism in a sibling or parent, especially at a relatively young age, e.g. younger than 50 years).	If genetic predisposition is suspected, the woman should be referred to a specialist for counselling before any decision about using a CHC is made.
Other diseases linked to VTE.	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease
Increasing age	Especially above 35 years of age

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 especially during 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)

At the onset of symptoms, the user is advised to seek immediate medical assistance and to inform the nursing staff that they are using a CHC.

In the event of deep vein thrombosis (DVT), the following symptoms may occur:

- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg, which may only be noticed when standing or walking;
- warmth of the affected leg; red or discoloured skin on the leg.

In the event of pulmonary embolism (PE), the following symptoms may occur:

- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden onset of cough, possibly in combination with haemoptysis;
- stabbing chest pain;

- severe light-headedness or dizziness;
- rapid or irregular heartbeat.

Some of these symptoms (e.g. “shortness of breath”, “cough”) are non-specific and may be misinterpreted as more common and less serious events (e.g. as respiratory tract infections).
Other signs of vascular occlusion may be sudden pain, as well as swelling and slight bluish discoloration of an extremity.
If the vascular occlusion occurs in the eye, the symptoms can range from painless blurred vision to loss of vision. In some cases, loss of vision occurs very suddenly.

Risk of arterial thromboembolism (ATE)
Epidemiological studies have associated the use of CHCs with an increased risk of arterial thromboembolism (myocardial infarction) or 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 cerebrovascular accident in CHC users is increased in women with risk factors (see Table). Microgynon Fe is contraindicated in women with a serious or multiple risk factors for ATE which expose them to a 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 overall risk must be considered. If the benefit/risk ratio is unfavourable, no CHCs may be prescribed (see section 4.3).

Table: Risk factors for ATE

Risk factor	**Note**
Increasing age	Especially above 35 years of age
Smoking	Women should be advised not to smoke if they wish to use a CHC. Women over 35 years who continue to smoke are strongly recommended to use another method of contraception.
Hypertension	
Obesity (body mass index over 30 kg/m²)	The risk increases significantly with increasing BMI. Particularly important in women with additional risk factors.
Family predisposition (any venous thromboembolism in a sibling or parent, especially at a relatively young age, e.g. younger than 50 years).	If genetic predisposition is suspected, the woman should be referred to a specialist for counselling before any decision about using a CHC is made.
Migraine	An increase in the frequency or severity of migraine whilst using CHCs (which may precede a cerebrovascular event) may be a reason for immediate discontinuation.
Other diseases linked to undesirable vascular events.	Diabetes mellitus, hyperhomocysteinaemia, heart valve disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE
At the onset of symptoms, women are advised to seek immediate medical assistance and to inform the nursing staff that they are using a CHC.
In the event of a cerebrovascular accident, the following symptoms may occur:
- sudden numbness or weakness of the face, arm or leg, especially on one side of the body;

- sudden difficulties in walking, dizziness, loss of balance or coordination problems;
- sudden confusion, difficulties in speaking or understanding;
- sudden visual disturbances in one or both eyes;
- sudden, severe or prolonged headache of unknown origin;
- loss of consciousness or fainting with or without seizure.

Transient symptoms indicate a transient ischaemic attack (TIA).
In the event of myocardial infarction (MI), the following symptoms may occur:
- pain, discomfort, pressure, heaviness, tightness or fullness in the chest, arm or below the sternum;
- discomfort radiating to the back, jaw, neck, arm or stomach;
- bloating, indigestion or choking sensation;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety or shortness of breath;
- rapid or irregular heartbeats.

Tumours
Some epidemiological studies indicate that long-term COC use is associated with an increased risk of cervical cancer. However, there is still disagreement as to the extent to which this finding can also be attributed to sexual behaviour and other factors, e.g. the human papillomavirus (HPV).

A meta-analysis, based on 54 epidemiological studies, has revealed that women currently taking COCs have a slightly increased breast cancer risk (RR = 1.24). This increased risk gradually regresses within 10 years upon discontinuation of COCs. As breast cancer occurs relatively rarely in women below 40 years, the number of additional breast cancer cases in previous or current oral contraceptive users is small compared to the overall risk of breast cancer. These studies provide no evidence of the causes.

The observed increased risk may be attributable to earlier diagnosis of breast cancer in users, the biological effects of COCs or even a combination of both. Tumours diagnosed in users seem to be at an earlier clinical stage than tumours diagnosed in non-users.

In rare cases, benign and, even more rarely, malignant liver tumours have been observed in COC users. In individual cases, these tumours have led to life-threatening intra-abdominal bleeding. If severe epigastric discomfort, hepatomegaly or signs of intra-abdominal bleeding occur in users of oral contraceptives, a hepatic tumour should be included in the differential diagnostic considerations.

Other disorders
Women with hypertriglyceridaemia, or a positive family history thereof, may be at increased risk of developing pancreatitis whilst taking COCs.

Although a slight increase in blood pressure has been reported in many women using COCs, clinically relevant blood pressure elevations are rare. Only in these rare cases is immediate discontinuation of COC use warranted. To date, no systematic connection has been established between taking COCs and clinical hypertension. If blood pressure readings are constantly elevated in patients with pre-existing hypertension concomitantly taking an oral contraceptive, or if there is a significant increase in blood pressure and antihypertensive therapy shows no effect in such cases, the COC must be discontinued. If deemed appropriate, COC use can be resumed as soon as blood pressure values have returned to normal on antihypertensive therapy.

The following disorders are reported to occur or deteriorate both during pregnancy and during COC use, but it has not been possible to prove any connection with COC use: cholestatic jaundice and/or pruritus, cholelithiasis, porphyria, systemic lupus erythematosus, haemolytic-uraemic syndrome, Sydenham’s chorea; herpes gestationis, otosclerosis-related hearing loss, depressive moods.

Exogenously administered oestrogens may precipitate or exacerbate symptoms of hereditary and acquired angioedema.

Acute or chronic liver dysfunction may necessitate discontinuation of COC use until liver function values have returned to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus having occurred in a previous pregnancy or during previous use of steroid sex hormones also requires COC discontinuation.

Although COCs can have an effect on peripheral insulin resistance and glucose tolerance, there are no indications of any need to change the therapeutic regimen in diabetics using low-dose COCs (<50 micrograms of ethinylestradiol). However, diabetics must be carefully monitored especially during the initial period of COC use.

Exacerbation of endogenous depression, epilepsy, Crohn's disease and ulcerative colitis has been reported with 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 doctor in the event of mood changes or depressive symptoms, including shortly after initiating treatment.

Chloasma may occasionally occur during COC use, especially in women with a history of chloasma gravidarum. Users with this predisposition should therefore avoid exposure to direct sunlight or ultraviolet light whilst taking COCs.

This medicinal product contains sucrose and lactose. Patients with rare hereditary problems of galactose or fructose intolerance, lactase deficiency, glucose-galactose malabsorption or sucrose-isomaltase deficiency should not take Microgynon Fe.

Medical examination/consultation

Prior to initiating or resuming treatment with Microgynon Fe, a complete medical history (including family history) must be taken and pregnancy excluded. Blood pressure should be measured and a physical examination performed, guided by the contraindications (see section 4.3) and warnings (see section 4.4). It is important to draw the woman's attention to the information on venous and arterial thrombosis, including the risk of Microgynon Fe compared to other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of suspected thrombosis.
The user should also be instructed to read the package leaflet carefully and to follow the advice given therein. The frequency and nature of examinations should be in accordance with current examination guidelines and individually tailored to the woman.
Users should be informed that hormonal contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of COCs may be impaired if tablets have been missed, in the event of vomiting or diarrhoea or if certain other medicinal products are concurrently taken.

Irregular bleeding

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur especially in the first few months of use. Assessment of such intermenstrual bleeding is therefore meaningful only after an adaptation phase of about three cycles. In more than 50% of users of oral contraceptives containing ethinylestradiol/levonorgestrel, bleeding (spotting or breakthrough bleeding) has been observed during the first six treatment cycles.

If such irregular bleeding persists or occurs after previously regular cycles, non-hormonal causes should be considered and appropriate diagnostic measures instituted to exclude malignancy or pregnancy. Curettage may be necessary.

Withdrawal bleeding may not occur in some users whilst taking the inactive tablets. If the COC has been taken as described in section 4.2, pregnancy is unlikely. However, if tablets have not been taken as directed prior to the first absent withdrawal bleed, or if withdrawal bleeding is absent for a second time, pregnancy must be definitely excluded before use of the COC is continued.

4.5 Interaction with other medicinal products and other forms of interaction

Note: For each co-prescribed medicinal product, the information for healthcare professionals should be reviewed for possible interactions.

Influence of other medicinal products on Microgynon Fe
Interactions can occur with medicinal products that induce microsomal enzymes. This may result in increased clearance of sex hormones and lead to breakthrough bleeding and/or contraceptive failure.

Enzyme induction may be observed within a few days of treatment. The maximum enzyme-induced effect is normally observed within a few weeks. The enzyme-induced effect may last for up to 4 weeks after treatment is finished.

Women treated with any of these medicinal products should temporarily use a barrier method or another contraceptive method in addition to the COC. The barrier method must be used throughout the entire period whilst these medicines are being used and for up to 28 days after discontinuation of treatment. If it is necessary to continue taking any of these medicines upon completion of a COC blister, tablet-taking from the next COC blister should be commenced immediately without the usual tablet-free interval.

Reduced absorption: medicinal products that increase gastrointestinal motility, e.g. metoclopramide, may reduce the absorption of hormones.

Substances that increase the clearance of COCs (reduced COC efficacy due to enzyme induction) e.g.:
Phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly also oxcarbazepine, topiramate, felbamate and griseofulvin. Herbal preparations containing St. John's wort (*Hypericum perforatum*) should not be used concomitantly with Microgynon Fe tablets, as they may reduce the contraceptive effectiveness of Microgynon Fe. There have been reports of breakthrough bleeding and unintentional pregnancies. The enzyme-inducing effect may persist for up to two weeks after cessation of treatment with St. John's wort.

Substances with various effects on the clearance of COCs, e.g. ritonavir, nevirapine
When co-administered with COCs, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease the plasma concentrations of oestrogens and progestogens. These changes can be clinically relevant in some cases.

Substances that increase the active substance concentrations of COCs (enzyme inhibitors):
Potent 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 oestrogen or progestogen or both.

Etoricoxib, at dosages of 60 to 120 mg/day, was shown to increase the plasma concentrations of ethinylestradiol by 1.4- or 1.6-fold, when COCs containing 35 micrograms of ethinylestradiol are concomitantly taken.

Influence of COCs on other medicinal products
Troleandomycin can increase the risk of intrahepatic cholestasis when co-administered with COCs.

COCs can influence the metabolism of other medicinal products. Elevated plasma concentrations of ciclosporin have been observed in women concurrently taking oral contraceptives. COCs can induce the metabolism of lamotrigine and hence lead to plasma levels of lamotrigine below the therapeutic range.

In vitro, ethinylestradiol is a reversible inhibitor of CYP 2C19, CYP 1A1 and CYP1A2, as well as a mechanism-based inhibitor of CYP 3A4/5, CYP 2C8 and CYP 2J2. In clinical studies, use of a hormonal contraceptive containing ethinylestradiol led to no or only a slight increase in the plasma concentrations of CYP3A4 substrates (e.g. midazolam), while the plasma concentrations of CYP 1A2 substrates were slightly (e.g. theophylline) or moderately (e.g. melatonin and tizanidine) increased.

Pharmacodynamic interactions
During clinical trials with patients treated for hepatitis C virus infections (HCV) with 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).

Microgynon Fe users must therefore switch to an alternative method of contraception (e.g. progestogen-only contraception or non-hormonal barrier methods) prior to starting therapy with these drug regimens. Microgynon Fe can be restarted 2 weeks following completion of treatment with these drug regimens.

Other forms of interaction

Laboratory tests
The use of steroid contraceptives may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, as well as the plasma levels of (carrier) proteins (e.g. corticosteroid-binding globulin and lipid/lipoprotein fractions), parameters of carbohydrate metabolism, as well as coagulation and fibrinolysis parameters. However, these changes generally remain within the normal range.

4.6 Fertility, pregnancy and lactation

Pregnancy
Microgynon Fe is not indicated during pregnancy. If pregnancy occurs during use of Microgynon Fe, the product must be withdrawn immediately.

In most of the epidemiological studies, no increased risk of malformations was found in children whose mothers had taken combined oral contraceptives before pregnancy, or any teratogenic effect when combined oral contraceptives were inadvertently taken during early pregnancy.

Breastfeeding
COCs can affect lactation, as they can reduce the quantity of breast milk and alter its composition. COC use is therefore not recommended until the mother has completely weaned her infant. Small amounts of contraceptive steroids and/or their metabolites may be excreted in breast milk. These amounts might adversely affect the infant.

The increased VTE risk in the postpartum period should be considered prior to reuse after a break in administration (see sections 4.2 and 4.4).

4.7 Effects on ability to drive and use machines

Microgynon Fe has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most common adverse reactions associated with the use of EE/LNG-containing combined oral contraceptives are headache, spotting and intermenstrual bleeding.

Other adverse reactions reported in users of EE/LNG-containing oral combined hormonal contraceptives, to which Microgynon Fe also belongs, are:

Organ system	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (frequency cannot be estimated from the available data)
Eye disorders			Contact lens intolerance	
Gastrointestinal disorders	Nausea, abdominal pain	Vomiting, diarrhoea		
Immune system disorders			Hypersensitivity	Exacerbation of symptoms of hereditary and acquired angioedema
Investigations	Weight gain		Weight loss	
Metabolism and nutrition disorders		Fluid retention		
Nervous system disorders	Headache	Migraine		
Psychiatric disorders	Depressive mood, mood lability	Reduced libido	Increased libido	
Reproductive system and breast disorders	Breast tenderness, mastodynia	Breast swelling	Mammary gland secretion, vaginal secretion	
Skin and subcutaneous tissue disorders		Exanthem, urticaria	Erythema nodosum, erythema multiforme	
Vascular disorders			Venous thromboembolism (VTE), Arterial thromboembolism (ATE)*	

* The most appropriate MedDRA term (version 7.0) to describe a certain adverse reaction is listed. Synonyms or related terms are not listed, but should also be taken into account.

Description of selected adverse reactions

In CHC users, an increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischaemic attacks, venous thrombosis and pulmonary embolism, has been observed, which are discussed in more detail in section 4.4

The following serious adverse reactions have been reported in women using COCs and are described in section 4.4:

- venous thromboembolic disorders;
- arterial thromboembolic disorders;
- cervical cancer;
- hypertension;
- hypertriglyceridaemia;
- effects on peripheral insulin resistance and glucose tolerance;
- hepatic tumours;
- hepatic dysfunction;
- chloasma;
  Crohn's disease, ulcerative colitis;
- epilepsy;
- migraine;
- endometriosis, uterine fibroids;
- porphyria;
- systemic lupus erythematosus;
- herpes gestationis;
- Sydenham's chorea;
- haemolytic-uraemic syndrome;
- cholestatic jaundice
- otosclerosis.

The frequency of breast cancer diagnosis is slightly increased among COC users. As breast cancer rarely occurs in women under 40 years, the risk of contracting breast cancer is low compared with the overall risk. There is no known causal relationship with COC use. For further information, see sections 4.3 and 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

There have been no reports of serious adverse reactions as a result of overdose. Symptoms that may be caused by overdose are nausea, vomiting and unexpected bleeding. If they accidentally take this medicinal product, vaginal bleeding may even occur in young girls who have not yet had their first period. There are no antidotes. Treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: progestogens and oestrogens, fixed combinations,
ATC code: G03AA07

The contraceptive action of COCs is based on the interaction of various factors. The most important of these factors are inhibition of ovulation and changes in cervical mucus.

Clinical trials have been performed on 2,498 women aged between 18 and 40 years. The Pearl Index calculated from these trials was 0.69 (95% confidence interval 0.30 – 1.36) based on 15,026 cycles.

5.2 Pharmacokinetic properties

Levonorgestrel

Absorption
Levonorgestrel is rapidly and completely absorbed after oral administration. Peak serum levonorgestrel concentrations of about 2.3 ng/mL are reached about 1.3 hours post-ingestion. Bioavailability is nearly 100%.

Distribution
Levonorgestrel is bound to serum albumin and sex hormone-binding globulin (SHBG). Only 1.1% of the total serum drug concentration is present as free steroid; about 65% is bound specifically to SHBG and about 35% non-specifically to albumin. The rise in SHBG induced by ethinylestradiol influences the relative distribution of levonorgestrel in various protein fractions. Induction of the binding protein causes an increase in the SHBG-bound fraction and a decrease in the albumin-bound fraction. The apparent volume of distribution of levonorgestrel is 129 L after a single dose.

Biotransformation
Levonorgestrel is extensively metabolised. The major metabolites in plasma are unconjugated and conjugated forms of 3α, 5β-tetrahydro-levonorgestrel. Based on *in vitro* and *in vivo* studies, CYP3A4 is the main enzyme involved in the metabolism of levonorgestrel. The metabolic clearance rate from serum is approximately 1.0 mL/min/kg.

Elimination
The serum levels of levonorgestrel decline in two phases. The terminal phase is characterised by a half-life of approximately 25 hours.
Levonorgestrel is not excreted in unchanged form. The ratio of urinary to biliary excretion of its metabolites is around 1:1. The half-life of metabolite excretion is about 1 day.

Steady state
During continuous use of Microgynon Fe, levonorgestrel levels in serum are reduced by about threefold and reach their steady state during the second half of the treatment cycle. The pharmacokinetics of levonorgestrel is affected by serum SHBG levels, which are increased by 1.5- to 1.6-fold during the use of oestradiol. Hence, the clearance rate from serum and the volume of distribution at steady state are slightly reduced (0.7 mL/min/kg or about 100 L).

Ethinylestradiol

Absorption
Ethinylestradiol is rapidly and completely absorbed after oral administration. Peak serum concentrations of about 50 pg/mL are reached about 1–2 hours after tablet ingestion. During absorption and the first-pass hepatic metabolism, ethinylestradiol is extensively metabolised, leading to a mean oral bioavailability of about 45% (interindividual variation of about 20-65%).

Distribution
Ethinylestradiol is predominantly (about 98%) but not specifically bound to serum albumin and induces a rise in the serum concentrations of SHBG. The apparent volume of distribution of ethinylestradiol is 2.8–8.6 L/kg.

Biotransformation
Ethinylestradiol is mainly degraded by enteral and hepatic first-pass metabolism. Ethinylestradiol and its oxidative metabolites are mainly conjugated with glucuronide or sulphate. The metabolic clearance rate is reported to be 2.3–7 mL/min/kg.

Elimination
The serum levels of ethinylestradiol decline in two phases, which are characterised by half-lives of about 1 hour and 10–20 hours, respectively.
Ethinylestradiol is not excreted in unchanged form. The metabolites are excreted via the urine and bile at a ratio of 4:6. The half-life is approximately 1 day.

Steady state
After continuous use of Microgynon Fe, the ethinylestradiol concentration in serum increases approximately twofold. Due to the daily administration and the variable half-life in the terminal phase of serum clearance, steady state is reached after about 1 week.

5.3 Preclinical safety data

Preclinical studies (on general toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction) revealed no indications of any further effects other than those that can already be explained by the known hormone profile of ethinylestradiol or levonorgestrel.

However, it should be considered that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active tablets:
Tablet core:
Lactose monohydrate, maize starch, povidone K25, talc, magnesium stearate (Ph.Eur.) [vegetable]

Tablet coating:
Sucrose, povidone K90, macrogol 6000, calcium carbonate, talc, glycerol 85%, montan glycol wax, titanium dioxide (E 171), yellow iron oxide (E 172)

Inactive tablets:
Tablet core:
Ferrous fumarate, lactose monohydrate, maize starch, povidone K25, talc, magnesium stearate

Tablet coating:
Sucrose, povidone 700,000, macrogol 6000, calcium carbonate, talc, titanium dioxide, ferric hydroxide oxide, montanglycol wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

Each blister contains 21 beige-coloured, active tablets and 7 brown, inactive tablets.
Microgynon Fe is available in packs of 1 blister strip, containing 28 tablets
(PVC/PPE.EVOH.PE/PCTFE/aluminium)

6.6 Special precautions for disposal

Tablets you no longer use should not be disposed of via the regional wastewater system. Please take the packs to your pharmacy or ask the pharmacist for information about suitable disposal options. These measures will help protect the environment.

7. MANUFACTURED BY

Bayer AG
Physical address: Muellerstr. 178, 13353 Berlin
Postal address: 13342 Berlin,
German

8.DATE OF REVISION OF THE TEXT

October 2022

REC 30695+20788

9. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription