National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

COMBIFEM

(Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Combipack of

21 tablets of Levonorgestrel and Ethinylestradiol tablets

Each sugar-coated White tablet contains:

Levonorgestrel Ph. Eur. 150 mcg
Ethinylestradiol Ph. Eur 30 mcg

Excipients Q.S.
Colour: Titanium dioxide

And 7 tablets of Ferrous Fumarate Tablet BP

Each Sugar-coated brown tablet contains:

Ferrous Fumarate BP 75 mg
(Equivalent to Ferrous iron: 24.375 mg)

Excipients Q. S.

Color: Red Oxide of Iron, Titanium dioxide

Excipients with known effect:

Levonorgestrel and Ethinylestradiol tablets

Lactose Monohydrate 52.353 mg
Sucrose 14.187 mg

Ferrous Fumarate Tablet
Sucrose 16.10 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Levonorgestrel and Ethinylestradiol tablets

White, Circular, biconvex, sugar coated tablets.

Ferrous Fumarate Tablet

Brown, Circular, biconvex, sugar coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception and the recognised gynaecological indications for such oestrogen-progestogen combinations.

The decision to prescribe Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg, should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg compares with other combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Tablets must be taken orally at about the same time every day, with some liquid if necessary, starting from the top left hand corner of the pack i.e the first white tablet. When the white tablets are finished, the patient should start taking the brown tablets.

First treatment cycle: 1 tablet daily **for 28 days**, starting on the first day of the menstrual cycle. 21 white (active) tablets are taken followed by 7 brown (inactive) tablets. Contraceptive protection begins immediately.

Subsequent cycles: Tablet-taking is continuous, which means 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 Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg

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.

Changing from 21-day combined oral contraceptives:

The first tablet of Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg should be taken on the first day immediately after the end of the previous oral contraceptive course. Additional contraceptive precautions are not required.

Changing from a combined Every Day pill (28 -day pill):

Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg should be started after taking the last active tablet from the previous Every Day pill pack. The first Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg is taken the next day. Additional contraceptive precautions are not then required.

Switching from another combined hormonal contraceptive (vaginal ring, transdermal patch)

The user should preferably start taking Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg on the day after removal of the ring or patch, but by no later than the day after the usual ring-free or patch-free days of the previous product.

Changing from a progestogen-only pill (POP):

The first tablet of Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg should be taken on the first day of bleeding, even if a POP has already been taken on

that day. Additional contraceptive precautions are not then required. The remaining progestogen-only pills should be discarded.

Switching from a progestogen-only product (injection, implant) or an intrauterine system (IUS)

In women previously having a progestogen implant or intrauterine system, 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.

Post-partum and use:

After pregnancy, oral contraception can be started 21 days after a vaginal delivery, provided that the patient is fully ambulant and there are no puerperal complications. Additional contraceptive precautions will be required for the first 7 days of tablet taking to ensure adequate contraceptive cover if early ovulation has occurred.

Since the first post-partum ovulation may precede the first bleeding, another method of contraception should be used in the interval between childbirth and the first course of tablets.

For use during breast-feeding, see section 4.6.

Post-abortum use

Following a first-trimester abortion

After a first-trimester abortion, oral contraception may be started immediately in which case no additional contraceptive precautions are required.

Following a second-trimester abortion

Tablet-taking should commence on days 21 to 28 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.

Special circumstances requiring additional contraception

Incorrect administration: Errors in taking the 7 brown (inactive) tablets can be ignored. A single delayed white (active) tablet should be taken as soon as possible, and if this can be done within 12 hours of the correct time, contraceptive protection is maintained.

Management of missed tablets

Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg 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 Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with

ferrous fumarate tablets 75 mg. 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 Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg 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 (ATE)
  - 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, e.g. active viral hepatitis and severe cirrhosis 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.

Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg is contraindicated for concomitant use with medicinal products containing ombitasvir/ paritaprevir/ ritonavir, dasabuvir, glecaprevir/pibrentasvir and ofosbuvir/velpatasvir/voxilaprevir (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Warnings

The suitability of Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg 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 Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg 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. **Products that contain levonorgestrel, such as Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg, norgestimate or norethisterone are associated with the lowest risk of VTE. The decision to use Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg 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 Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg 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.

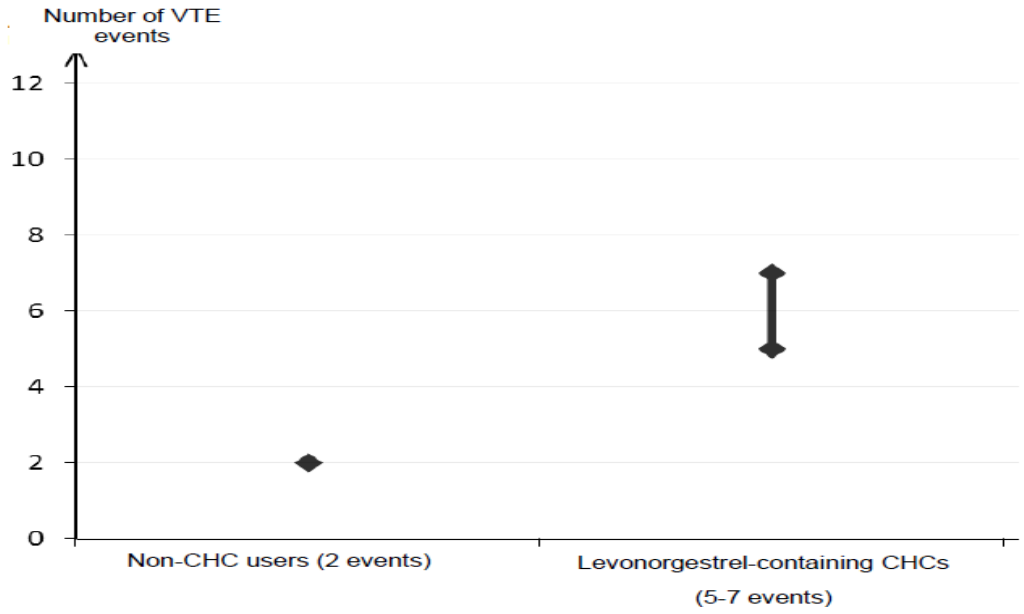
The number of VTEs per year with low-dose CHCs is lower than the expected number during pregnancy or in the postpartum period.

VTEs are fatal in 1-2% of cases.

[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

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.

Annual number of VTE events per 10,000 women



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).

Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg 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	**Comment**
Obesity (body mass index over 30 kg/m²)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: Temporary immobilisation including air travel > 4 hours can also be a risk factor for VTE,	In these situations it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilization. Another method of contraception should be used to avoid unintentional pregnancy

particularly in women with other risk factors.	Antithrombotic treatment should be considered if Levonorgestrel 150 mcg and Ethinylestradiol 30 mcg Tablets has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease
Increasing age	Particularly above 35 years

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The increased risk of thromboembolism in pregnancy and 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. 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 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). Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg 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	**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.

Tumours

Numerous epidemiological studies have been reported on the risks of ovarian, endometrial, cervical and breast cancer in women using combined oral contraceptives. The evidence is clear that high dose combined oral contraceptives offer substantial protection against both ovarian and endometrial cancer. However, it is not clear whether low dose COCs confer protective effects to the same level.

• *Breast cancer*

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COCs). 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 additional breast cancers diagnosed in current users of COCs or in women who have used COCs in the last ten years are more likely to be localised to the breast than those in women who never used COCs.

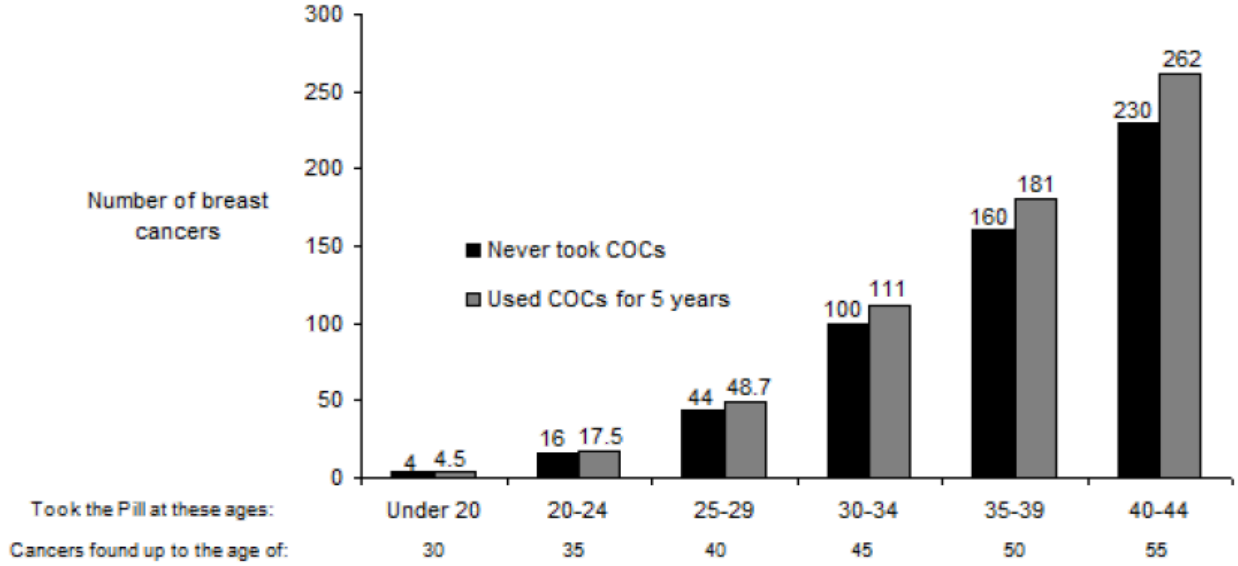
Breast cancer is rare among women under 40 years of age whether or not they take COCs. Whilst this background risk increases with age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer (see bar chart).

The most important risk factor for breast cancer in COC users is the age women discontinue the COC; the older the age at stopping, the more breast cancers are diagnosed.

Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping COC use such that by 10 years there appears to be no excess.

The possible increase in risk of breast cancer should be discussed with the user and weighed against the benefits of COCs taking into account the evidence that they offer substantial protection against the risk of developing certain other cancers (e.g. ovarian and endometrial cancer).

Estimated cumulative number of breast cancers per 10,000 women diagnosed in 5 years of use and upto 10 years after stopping COCs, compared with number of breast cancers diagnosed in 10,000 women who had never used COCs



·*Cervical Cancer*

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 behavior including use of barrier contraceptives.

• *Liver Cancer*

In rare cases benign and, in even rarer cases, malignant liver tumours leading in isolated cases to life - threatening intraabdominal haemorrhage have been observed after the use of hormonal substances such as those contained in Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, the possibility of a liver tumour should be included in the differential diagnosis.

Other conditions

The possibility cannot be ruled out that certain chronic diseases may occasionally deteriorate during the use of combined oral contraceptives

• *Known hyperlipidaemias*

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

Women with hyperlipidaemias are at an increased risk of arterial disease (see section 4.4 'Risk of arterial thromboembolism (ATE)'). However routine screening of women on COCs is not appropriate.

• *Blood pressure*

Hypertension is a risk factor for stroke and myocardial infarction (see section 4.4 'Risk of arterial thromboembolism (ATE)'). Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if sustained hypertension develops during the use of a COC, antihypertensive treatment should normally be instigated at a level

of 160/100 mm Hg in uncomplicated patients or at 140/90 mm Hg in those with target organ damage, established cardiovascular disease, diabetes or with increased cardiovascular risk factors.
Decisions about the continued use of the COC should be made at lower BP levels, and alternative contraception may be advised.

• *Conditions which deteriorate in pregnancy or during previous COC use*

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use. Consideration should be given to stopping Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg if any of the following occur during use:

• jaundice and/or pruritus related to cholestasis
• COCs may increase the risk of gallstone formation and may worsen existing disease.
• systemic lupus erythematosus
• herpes gestationis
• otosclerosis-related hearing loss
• sickle cell anaemia
• renal dysfunction
• hereditary angioedema
• any other condition an individual woman has experienced worsening of during pregnancy or previous use of COCs.

• *Angioedema*

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

• *Disturbances of liver function*

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 occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

• *Diabetes (without vascular involvement*)

Insulin-dependent diabetics without vascular disease can use COCs. However it should be remembered that all diabetics are at an increased risk of arterial disease and this should be considered when prescribing COCs. Diabetics with existing vascular disease are contraindicated from using COCs (see section 4.3 Contraindications).

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.

• *Psychiatric disorders*

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*

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.

• *Menstrual Changes*

Reduction of menstrual flow: This is not abnormal and it is to be expected in some patients. Indeed, it may be beneficial where heavy periods were previously experienced.

Missed menstruation: Occasionally, withdrawal bleeding may not occur at all. If the tablets have been taken correctly, pregnancy is very unlikely. If withdrawal bleeding fails to occur at the end of a second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

Intermenstrual bleeding: 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. This may include curettage.

Some women may experience amenorrhoea or oligomenorrhoea after discontinuation of oral contraceptives, especially when these conditions existed prior to use. Women should be informed of this possibility.

- *Lactose and Sucrose Intolerance*

Each active (white) tablet of this medicinal product contains 52.353 mg lactose and 14.187 mg sucrose per tablet. Each inactive (brown) tablet contains 16.10 mg sucrose per tablet.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, fructose intolerance or glucose-galactose malabsorption or sucrase-isomaltase should not take this medicine.

• *Reduced efficacy*

The efficacy of COCs may be reduced, in the event of missed tablets, vomiting or diarhhoea, or concomitant medication.

ALT elevations

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 frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs) . ALT elevations have also been observed with HCV anti-viral medicinal products containing glecaprevir/pibrentasvir and sofosbuvir/velpatasvir /oxilaprevir (see sections 4.3 and 4.5).

Medical examination/consultation

Prior to the initiation or reinstitution of Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg, 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 Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with

ferrous fumarate tablets 75 mg compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

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

Undiagnosed vaginal bleeding that is suspicious for underlying conditions should be investigated.

Conditions which require strict medical supervision

The decision to prescribe the COC must be made using clinical judgement and in consultation with the woman.

Exacerbation or first appearance of any of these conditions or risk factors may indicate that use of the oral contraceptive should be discontinued. The woman should contact her physician, who should then decide on whether COC use should be discontinued:

- Diabetes mellitus with mild vascular disease or mild nephropathy, retinopathy or neuropathy
- Hypertension that is adequately controlled, i.e. systolic >140 to159 mm Hg or diastolic > 90 to 94 mm Hg (see also Section 4.4 'Reasons for stopping oral contraception immediately')
- porphyria
- obesity
- migraine
- cardiovascular diseases

Reasons for stopping oral contraception immediately:

When stopping oral contraception non-hormonal contraception should be used to ensure contraceptive protection is maintained.

1. Occurrence for the first time, or exacerbation, of migrainous headaches or unusually frequent or unusually severe headaches
2. Sudden disturbances of vision, of hearing or other perceptual disorders
3. First signs of thrombosis or blood clots (e.g. unusual pains in or swelling of the leg(s), stabbing pains on breathing or coughing for no apparent reason). Feeling of pain and tightness in the chest
4. At least four weeks before an elective major operation (e.g. abdominal, orthopaedic), any surgery to the legs, medical treatment for varicose veins or prolonged immobilisation, e.g. after accidents or surgery. Do not restart until 2 weeks after full ambulation. In case of emergency surgery, thrombotic prophylaxis is usually indicated e.g. subcutaneous heparin
5. Onset of jaundice, hepatitis, itching of the whole body
6. Significant rise in blood pressure
7. Severe upper abdominal pain or liver enlargement
8. Clear exacerbation of conditions known to be capable of deteriorating during oral contraception or pregnancy (see section 4.4 'Conditions which deteriorate in pregnancy or during previous COC use' under 'Other conditions')

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.

• Interactions

Enzyme inducers

Interactions can occur with drugs that induce microsomal enzymes (especially cytochrome P450 3A4) which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

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 short term 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 methods used runs beyond the last active tablet, the user should finish taking all the active tablets, discard the inactive tablets and start a new pack of Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg the next day with an appropriate active tablet. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed during the tablet free interval following the end of the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

For women receiving long-term therapy with enzyme inducers, another method of contraception should be used.

The following have been shown to have clinically important interactions with COCs:

Anticonvulsants: barbiturates (including phenobarbitone), primidone, phenytoin, carbamazepine, oxcarbazepine, topiramate.

Antibiotics/antifungals: griseofulvin, rifampacin.

Herbal remedies: St John's wort (*Hypericum perforatum*)

Antiretroviral agents: ritonavir, nelfinavir, nevirapine.

Note: There are other antiretroviral agents that may increase plasma concentration of sex hormones.

Substances decreasing the clearance of COCs (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), and macrolides (e.g. erythromycin) can increase plasma concentrations of the oestrogen 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 on other drugs

Oral contraceptives may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin, tizanidine, theophylline) or decrease (e.g. lamotrigine).

Pharmacodynamic interactions

Concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir,

with or without ribavirin, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir, may increase the risk of ALT elevations (see sections 4.3 and 4.4).

Therefore, Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg-users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these drug regimens. Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg can be restarted 2 weeks following completion of treatment with these drug regimens.

• Laboratory tests

The use of oral contraceptives 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.

Laboratory staff should therefore be informed about oral contraceptive use when laboratory tests are requested.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg is not indicated during pregnancy. If pregnancy occurs during use of Microgynon 28, 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.

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).

Breastfeeding

The use of Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg during lactation may lead to a reduction in the volume of milk produced and to a change in its composition. Minute amounts of the active substances are excreted with the milk. These amounts may affect the child particularly in the first 6 weeks post-partum. Mothers who are breast-feeding may be advised instead to use another method of contraception.

4.7 Effects on ability to drive and use machines

Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions with Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg 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.

The following adverse events have been reported during use of ethinylestradiol / levonorgestrel:

System Organ Class	**Adverse events reported in clinical trials**			**Adverse events reported post marketing**
	Common (≥ 1/100)	**Uncommon (≥ 1/1000, < 1/100)**	**Rare (< 1/1000)**	
Eye disorders			contact lens intolerance	
Gastrointestinal disorders	nausea, abdominal pain	vomiting, diarrhea		Crohn's disease, ulcerative colitis
Immune system disorders			Hypersensitivity	exacerbation of hereditary angioedema
Investigations	Weight increased		Weight decreased	
Metabolism and nutrition disorders		Fluid retention		Hypertriglyceridemia
Nervous system disorders	Headache	Migraine		Exacerbation of chorea
Vascular disorders			Venous thromboembolism, Arterial thromboembolism	
Hepatobiliary disorders				Liver function disturbances
Psychiatric disorders	Depressive mood, mood altered	Reduced libido	Increased libido	

System Organ Class	Adverse events reported in clinical trials			Adverse events reported post marketing
	Common (≥ 1/100)	**Uncommon (≥ 1/1000, < 1/100)**	**Rare (< 1/1000)**	
Reproductive system and breast disorders	breast pain, breast tenderness	breast hypertrophy	vaginal discharge breast discharge	reduced menstrual flow, spotting, breakthrough bleeding and missed withdrawal bleeding, post pill amenorrhoea
Skin and sub - cutaneous tissue disorders		Rash, urticaria	Erythema nodosum, erythema multiforme	chloasma

Description of selected adverse reactions

In women using CHCs, 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, 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
- Strokes (e.g. transient ischemic attack, ischemic stroke, haemorrhagic stroke)
- Hypertension
- Liver tumours (benign and malignant)
- Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema

The frequency of diagnosis of breast cancer is very slightly increased among COC 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 'Contraindications' and 4.4 'Special warnings and precautions for use'.

Conditions reported to deteriorate with pregnancy or previous COC use

Jaundice and/or pruritus related to cholestasis; gallstone formation; systemic lupus erythematosus; herpes gestationis; otosclerosis-related hearing loss; sickle cell anaemia; renal dysfunction; hereditary angioedema; porphyria; cervical cancer.

Changes in glucose tolerance or effect on peripheral insulin resistance have been reported in women using COCs (see section 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 via the national reporting system.

4.9 Overdose

There have been no reports of serious effects from overdose. Overdosage may cause nausea, vomiting and, in females, withdrawal bleeding. Withdrawal bleeding may even occur in girls before their menarche, if they accidentally take the medicinal product.

There are no specific antidotes and treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, Progestogens and oestrogens, fixed combinations

ATC Code: G03AA07

Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg is an oestrogen-progestogen combination which acts by inhibiting ovulation by suppression of the mid-cycle surge of luteinizing hormone, the inspissation of cervical mucus so as to constitute a barrier to sperm, and the rendering of the endometrium unreceptive to implantation.

Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg also contain ferrous fumarate which is not a contraceptive but works as a blood forming repair ingredient by stimulating the formation of red blood cells (erythropoesis).

5.2 Pharmacokinetic properties

<u>Levonorgestrel</u>

Levonorgestrel is absorbed quickly and completely. Maximum active substance levels of approx. 3 ng/ml were reached in serum just one hour after ingestion of Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg. The serum concentrations subsequently fell in 2 phases with half-lives of around 0.5 hours and 20 hours. The metabolic clearance rate from plasma is approx. 1.5 ml/min/kg.

Levonorgestrel is eliminated not in unchanged form, but in the form of metabolites with a half-life of around one day and in almost equal proportions via the kidney and bile. Levonorgestrel is extensively metabolised. 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.

Levonorgestrel is bound to serum albumin and SHBG. Only around 1.5% of the respective total concentration is present in unbound form, while approx. 65% is bound to SHBG. The relative proportions (free, albumin-bound, SHBG-bound) depend on the concentration of SHBG. After induction of the binding protein, the portion bound to SHBG increases, while the free portion and that bound to albumin decreases.

After daily repeated ingestion, levonorgestrel accumulates by about the factor 2. A steady state is reached during the second half of the treatment cycle. The pharmacokinetics of levonorgestrel are dependent on the concentration of SHBG in plasma. Under treatment with Levonorgestrel 0.15 mg

and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg, an increase in the serum levels of SHBG effect a concomitant increase in the specific binding capacity and therefore also an increase in levonorgestrel serum levels.

The levonorgestrel serum levels do not change any further after 1 - 3 cycles of use owing to the fact that SHBG induction is concluded. Compared to a single administration, 3-4 fold higher levonorgestrel serum levels are reached in the steady state.
The absolute bioavailability of levonorgestrel amounts to almost 100%.
Approx. 0.1% of the maternal dose can be passed on to a baby with the breast milk.

Ethinylestradiol

Orally administered ethinylestradiol is absorbed quickly and completely. Ingestion of Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets with ferrous fumarate tablets 75 mg leads to maximum plasma levels of approx. 100 pg/ml after 1 - 2 hours. The substance concentration then falls in 2 phases for which half-lives of around 1 - 2 hours and about 20 hours have been determined. For technical reasons, these data can only be calculated at higher dosages.

An imaginary distribution volume of around 5 l/kg and a metabolic clearance rate from plasma of approx. 5 ml/min/kg have been determined for ethinylestradiol. Ethinylestradiol is bound non-specifically to serum albumin to the extent of 98%.

Ethinylestradiol is metabolised even during its absorption phase and during its first liver transit, leading to reduced and individually varying oral bioavailability. Ethinylestradiol is eliminated not in unchanged form, but in the form of metabolites with a half-life of around one day. The excretion ratio is 40 (urine): 60 (bile).
Because of the half-life of the terminal elimination phase from plasma, a steady state characterised by a 30 - 40% higher plasma substance level becomes established after approx. 5 - 6 daily administrations.

The absolute bioavailability of ethinylestradiol is subject to considerable interindividual variations. After oral ingestion, it amounts to around 40 - 60% of the dose.
In women with fully established lactation, around 0.02% of the maternal dose can be passed on to the baby with the breast milk.

Other drugs can have a negative or positive effect on the systemic availability of ethinylestradiol. No interaction with vitamin C takes place. On continuous use, ethinylestradiol induces the hepatic synthesis of CBG and SHBG, the extent of SHBG induction being dependent on the type and dose of the simultaneously administered progestogen.

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.

6.0 Pharmaceutical Particulars

6.1 List of Excipients

S. No.	Levonorgestrel and Ethinylestradiol	Ferrous Fumarate Tablets
1.	Lactose Monohydrate	Ferrous Fumarate
2.	Maize Starch	Maize Starch
3.	Povidone K-25	Polysorbate 80
4.	Talc	Methyl Paraben
5.	Magnesium Stearate	Propyl Paraben
6.	Povidone K-90	Sodium Starch Glycolate
7.	Glycerol	Purified Talc
8.	Sucrose	Magnesium Stearate
9.	Calcium Carbonate	Shellac
10.	Macrogol 6000	Isopropyl Alcohol
11.	Titanium Dioxide	Sodium Benzoate
12.	Carnauba Wax	Gum Acacia
13.	--	Sucrose
14.	--	Red oxide of iron
15.	--	Titanium Dioxide
16.	--	Carnauba Wax
17.	--	Chloroform

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30ºC. Keep out of reach of children.

6.5 Nature and contents of container

A blister pack of 28 Tablets.

6.6 Special precautions for disposal and other handling

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

7.0 APPLICANT/SUPPLIER

Supplier: Mylan Laboratories Limited
Plot No.: 1606 - 1609, G.I.D.C., Sarigam, Tal – Umergam,

Dist-Valsad – 396155, Gujarat, India.

8.0 FDA APPLICATION NUMBER

To be decided

9.0 DATE OF RENEWAL OF THE AUTHORISATION

To be decided

10.0 DATE OF REVISION OF THE TEXT

05/2020

References:

1. MICROGYNON® 30 ED (Levonorgestrel 150 micrograms and Ethinylestradiol 30 micrograms); Bayer plc; March 2020; Summary of Product Characteristics; emc; UK; Accessed on May 22nd 2020;

Accessed from https://www.medicines.org.uk/emc/product/1131/smpc.

2. MICROGYNON 28 (Levonorgestrel 150 micrograms and Ethinylestradiol 30 micrograms); EU Summary of Product Characteristics, (Jenapharm GmbH & Co. KG); July 2017; Accessed from

https://extranet.who.int/prequal/sites/default/files/RH082Part4v1.pdf. Accessed on 27th March, 2019