NAME OF THE MEDICINE

Microgynon 20 ED is a combined oral contraceptive (COC) tablet containing the synthetic oestrogen, ethinyloestradiol and the synthetic progestogen, levonorgestrel.

The chemical name for ethinyloestradiol is 19-nor-17α-pregna-1,3,5(10)-tien-20-yn-3, 17β-diol and has the following structural formula:

Chemical Formula: C_{20}H_{24}O_{2}
Molecular Weight: 296.41
Melting Point: 181–185°C
CAS No: 57-63-6

The chemical name for levonorgestrel is 13β-ethyl-17β-hydroxy-18, 19-dinor-17α-pregn-4-en-20-yn-3-one and has the following structural formula:

Chemical Formula: C_{21}H_{26}O_{2}
Molecular Weight: 312.45
Melting Point: 232 – 239°C
CAS No: 797-63-7

DESCRIPTION

Ethinyloestradiol is a white to creamy white, odourless, crystalline powder. It is practically insoluble in water and soluble in alcohol, chloroform, ether, vegetable oils and aqueous solutions of alkali hydroxides.
Levonorgestrel is a white or almost white, odourless or almost odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol, acetone and ether; soluble in chloroform; sparingly soluble in methylene chloride.

Each pink active tablet contains ethinylestradiol 20 µg and levonorgestrel 100 µg and the excipients: calcium carbonate, glycerol, glycol montanate, iron oxide red, iron oxide yellow, lactose, macrogol 6000, magnesium stearate, maize starch, povidone, pregelatinised starch, purified talc, sucrose and titanium dioxide.

Each white placebo tablet contains calcium carbonate, glycol montanate, lactose, macrogol 6000, magnesium stearate, maize starch, povidone, purified talc and sucrose.

**PHARMACOLOGY**

The hormonal components of Microgynon 20 ED inhibit ovulation by suppressing gonadotrophin release. Secondary mechanisms which may contribute to the effectiveness of Microgynon 20 ED as a contraceptive include changes in the cervical mucus (which increase the difficulty of sperm penetration) and changes in the endometrium (which reduce the likelihood of implantation).

**Pharmacokinetics**

A bioavailability study comparing Microgynon 20 to a microcrystalline solution was conducted. However as this study employed doses equivalent to three tablets instead of single tablet dosing for technical reasons, the pharmacokinetic information provided is derived from a single tablet pharmacokinetic study conducted in 20 women.

- **Ethinylestradiol**
  
  **Absorption**

  Orally administered ethinylestradiol is absorbed quickly and almost completely from the gastrointestinal tract but due to first-pass metabolism in gut mucosa and liver, the absolute bioavailability of ethinylestradiol is subject to considerable interindividual variations. After oral ingestion, it amounts to around 40–60% of the dose.

  Ingestion of Microgynon 20 ED leads to maximum plasma levels of approximately 50 pg/mL after 1 – 2 hours. The substance concentration then falls in at least 2 disposition phases with a terminal half-life of around 24 hours. For technical reasons, these data can only be calculated at higher dosages.

  **Distribution**

  Ethinylestradiol is bound non-specifically to serum albumin to about 98%. Ethinylestradiol does not bind to SHBG but induces SHBG synthesis.

  **Metabolism**

  Cytochrome P450 enzymes (CYP3A4) in the liver are responsible for the 2-hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and faecal excretion. Levels of CYP3A4 vary widely amongst individuals and may explain the variations in rates of ethinylestradiol 2-
Ethinyloestradiol is hydroxylated. Ethinyloestradiol is excreted in the urine and faeces as glucuronide and sulphate conjugates, and undergoes enterohepatic circulation.

**Elimination**

Ethinyloestradiol is eliminated not in unchanged form, but in the form of metabolites with a half-life of around 18 ± 4.7 hours at steady state. The excretion ratio is 40 (urine) : 60 (bile).

**Steady-state conditions**

According to the variable half-life of the terminal disposition phase from serum and the daily ingestion, steady-state serum levels of ethinyloestradiol will be reached after about one week.

- **Levonorgestrel**

**Absorption**

Levonorgestrel is absorbed quickly and completely. Maximum active substance levels of approximately 2.4 ng/mL were reached in serum approximately 1.0 – 1.3 hours after ingestion of Microgynon 20 ED. The absolute bioavailability of levonorgestrel amounts to almost 100%.

**Distribution**

Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only around 1.1% of the respective total concentration is present in unbound form, while approximately 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 to 75%, while the free portion and that bound to albumin decrease to around 0.8 and 25%, respectively.

**Metabolism**

Levonorgestrel is extensively metabolised. The major metabolites in plasma are the unconjugated and conjugated forms of 3α, 5β-tetrahydrolevonorgestrel. Additionally, based on in vitro and in vivo studies, CYP3A4 is the main enzyme involved in the oxidative metabolism of levonorgestrel.

The metabolic clearance rate, including the bound component, from plasma is approximately 1.0 mL/min/kg

**Elimination**

The serum concentrations subsequently fall in at least 2 disposition phases with a terminal half-life of around 24 hours.

Levonorgestrel is eliminated not in unchanged form, but in the form of metabolites with a half-life of approximately 28 ± 7 hours and in almost equal proportions via the kidney and bile.

**Steady-state conditions**

170215 Microgynon 20 ED PI
After daily repeated ingestion, levonorgestrel accumulates by about a factor of 3. A steady state is reached after approximately 11 days. The pharmacokinetics of levonorgestrel are nonlinear due to an increase in binding of levonorgestrel to SHBG which is attributed to increased SHBG levels that are induced by the daily administration of ethinyloestradiol. The levonorgestrel serum levels do not change any further after 1–3 cycles of use because SHBG induction is concluded.

CLINICAL TRIALS

An open-label, non-comparative multi-centre phase III clinical study was conducted in 820 women receiving Microgynon 20 for a planned individual maximum of 6 cycles. Six cycles were completed by 680 women. 4,400 cycles in which no alternative methods of contraception were used were available for the efficacy analysis. One pregnancy was reported. This represents an overall user-efficacy (typical user-efficacy) pregnancy rate of 0.32 per 100 women years (over 99% effective at preventing pregnancy). This rate includes patients who missed up to 3 tablets per cycle. The overall compliance (no missed tablets) was between 94.6% and 98.4% over the course of the study. Published data from a larger study with a similar preparation containing the same dosage of active ingredients in 1447 women, with 7720 cycles of exposure, report 5 pregnancies and an overall user-efficacy pregnancy rate of 0.84 per 100 women years, in women who missed up to 3 tablets consecutively per cycle or 5 non-consecutive tablets per cycle.

The overall user-efficacy pregnancy rates for Microgynon 20 and other forms of contraception from a number of non-comparative trials based on historical data are given below:

<table>
<thead>
<tr>
<th>Oral contraceptive</th>
<th>Overall user-efficacy (Pearl Index)</th>
<th>Effectiveness* at preventing pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microgynon 20</td>
<td>0.32</td>
<td>99.68%</td>
</tr>
<tr>
<td>100 µg levonorgestrel</td>
<td>0.30 – 0.35</td>
<td>99.65% – 99.7%</td>
</tr>
<tr>
<td>20 µg ethinyloestradiol</td>
<td>0.30 – 3.0</td>
<td>97.00% – 99.7%</td>
</tr>
<tr>
<td>100 µg levonorgestrel</td>
<td>0.84</td>
<td>99.16%</td>
</tr>
<tr>
<td>20 µg ethinyloestradiol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 µg levonorgestrel</td>
<td>0.30 – 0.35</td>
<td>99.65% – 99.7%</td>
</tr>
<tr>
<td>30 µg ethinyloestradiol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 µg levonorgestrel</td>
<td>0.30 – 3.0</td>
<td>97.00% – 99.7%</td>
</tr>
</tbody>
</table>

* 100%-(Pearl Index) = User effectiveness per 100 women years. (e.g. if 100 women took oral contraceptive tablets for 1 year the chance of an accidental pregnancy would be less than 1%).

Whilst the contraceptive efficacy of Microgynon 20 was 99.68% in a single study, the contraceptive efficacy of the levonorgestrel 100 µg/ethinyloestradiol 20 µg formulations ranges from 99.16–99.68%, compared historically with the contraceptive efficacy of 99.7% for 150 µg levonorgestrel/30 µg ethinyloestradiol tablets, this represents a similar up to 2-fold increase in the risk of pregnancy.
Cycle control was also evaluated by analysing cycle characteristics such as duration and intensity of withdrawal bleeding and the incidence of breakthrough bleeding and amenorrhoea. A total of 4400 cycles were valid for cycle control analysis; the overall incidence of inter-menstrual bleeding was low. Although there was no comparative study of the cycle control of Microgynon 20, compared with higher dosage oral contraceptives, cycle control data from historical studies with oral contraceptives containing higher doses of ethinyloestradiol and levonorgestrel are given in the table below:

<table>
<thead>
<tr>
<th>Dose*/ Study</th>
<th>Number of women</th>
<th>Number of cycles</th>
<th>Breakthrough Bleeding (% cycles)</th>
<th>Spotting (% cycles)</th>
<th>Amenorrhoea (% cycles)</th>
<th>Cycle length (days)</th>
<th>Mean length of menstruation (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100/20 Microgynon 20 (6 cycle)</td>
<td>820</td>
<td>4400</td>
<td>4.5</td>
<td>12.4</td>
<td>4.5</td>
<td>26 - 30</td>
<td>4.7</td>
</tr>
<tr>
<td>150/30</td>
<td>1130</td>
<td>11064</td>
<td>6.0</td>
<td>7.7</td>
<td>1.8</td>
<td>26 - 30 (mean 28.5)</td>
<td>4.3</td>
</tr>
<tr>
<td>150/30</td>
<td>325</td>
<td>3445</td>
<td>0.7</td>
<td>2.7</td>
<td>0.6</td>
<td>27 - 29</td>
<td>-</td>
</tr>
</tbody>
</table>

* Dose of levonorgestrel (µg)/ethinyloestradiol (µg). Note that the definitions of bleeding in these studies are not necessarily the same.

The length of withdrawal bleeding was 3 – 5 days for most patients (70%) (mean 4.7 days) and the intensity was scanty or normal for most subjects. Cycle length was between 26 and 30 days for most patients (up to 80%) with a tendency to be slightly shorter during the early cycles.

**INDICATIONS**

Microgynon 20 ED is indicated for the prevention of pregnancy.

**CONTRAINDICATIONS**

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

- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris)
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see PRECAUTIONS)
- History of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement
- Pancreatitis or a history thereof if associated with severe hypertriglyceridaemia
PRECAUTIONS

If any of the conditions/risk factors mentioned below are present, the benefits of COC use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start taking it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide on whether COC use should be discontinued.

Circulatory Disorders

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

Venous thromboembolism (VTE), manifesting as DVT and/or PE, may occur during the use of all COCs. The risk of VTE is highest during the first year a woman uses a COC. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study (EURAS\(^1\) and LASS\(^2\)) suggest that this increased risk is mainly present during the first 3 months.

A large prospective 3-armed cohort study has shown that the frequency of VTE diagnosis range from 8 to 10 per 10,000 woman years (WY) in low oestrogen dose (< 50 µg ethinyloestradiol) COC users. The most recent data suggest that the frequency of VTE diagnosis is approximately 4.4 per 10,000 WY in non-pregnant non-COC users and ranges from 20 to 30 per 10,000 WY in pregnancy or the post-partum period.

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

VTE may be life-threatening, or in 1–2% of cases may be fatal.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users.
Symptoms of a venous (includes PE and DVT) or arterial thrombotic / thromboembolic (includes myocardial infarction (MI), vascular occlusion and cerebrovascular accident) event can include: unilateral leg pain and/or swelling; pain or tenderness in the leg which may be felt only when standing or walking; increased warmth in the affected leg; red or discoloured skin on the leg; sudden, severe pain in the chest which may increase with deep breathing; 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; rapid or irregular heartbeat; sudden onset of unexplained shortness of breath or rapid breathing; sudden onset of coughing which may bring up blood; sudden, severe or prolonged headache with no known cause; sudden, partial or complete loss of vision; diplopia; sense of anxiety; dizziness; sudden confusion; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; ‘acute’ abdomen; fullness, indigestion or choking feeling; sweating; nausea; vomiting.

Some of these symptoms (e.g. “shortness of breath”, “coughing”) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

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

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

The risk of venous or arterial thrombotic / thromboembolic events or of a cerebrovascular accident increases with:

- age
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
- a positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any COC use
- obesity (body mass index over 30 kg/m²)
- overweight
- dyslipoproteinaemia
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation
- prolonged immobilisation (e.g. long haul flights), major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

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

The increased risk of thromboembolism during the puerperium must be considered (see Use in Pregnancy).
Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn’s disease or ulcerative colitis) and sickle cell disease.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the doctor should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low dose COCs (< 50 µg ethinyloestradiol).

**Tumours**

The most important risk factor for cervical cancer is persistent human papillomavirus (HPV) infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g. cervical screening and sexual behaviour including use of barrier contraceptives.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR =1.24) of having breast cancer diagnosed in women who are currently taking COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

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

**Other Conditions**

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

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC, it is prudent for the doctor to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.
The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham’s chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in women with diabetes taking low-dose COCs (containing < 50 µg ethinyloestradiol). However, women with diabetes should be carefully observed while taking COCs.

Crohn’s disease and ulcerative colitis have been associated with COC use.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

Each pink active tablet contains 33 mg of lactose and each white placebo tablet contains 34 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose free diet should take this amount into consideration.

Medical Examination/Consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the CONTRAINDICATIONS and PRECAUTIONS, and should be repeated periodically during the use of COCs. In general, an annual examination is recommended. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests.

Sexually Transmitted Infections (STIs) including Human Immunodeficiency Virus (HIV) infections and AIDS

Microgynon 20 ED is intended to prevent pregnancy. It does not protect against STIs, including HIV infections (AIDS). The woman should be advised that additional barrier contraceptive measures are needed to prevent transmission of STIs.

Reduced Efficacy
The efficacy of COCs may be reduced in the event of missed pink active tablets, vomiting or diarrhoea during active taking (see DOSAGE AND ADMINISTRATION) or concomitant medication (see INTERACTIONS WITH OTHER MEDICINES).

**Reduced Cycle Control**

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

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

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

**Carcinogenicity**

Long-term continuous administration of natural and synthetic oestrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver. A long-term study with levonorgestrel in dogs showed an increased incidence of mammary tumours, although a similar effect was not apparent in studies in mice, rats or monkeys. The occurrence of these mammary tumours in dogs may be due in part to a hormonal feedback mechanism. The clinical relevance of these findings is uncertain.

Numerous epidemiological studies have been conducted to determine the incidence of breast, endometrial, ovarian and cervical cancer in women taking COCs. Some of these studies have shown an increased relative risk of breast cancer in certain subgroups of COC users. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage. Some epidemiological studies also suggest that COC use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women, although there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as HPV. It must also be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumours (also see PRECAUTIONS).

**Genotoxicity**

There is limited evidence available in the literature suggesting that oestrogens may be weakly genotoxic at high doses. Ethinyloestradiol was negative in studies for DNA-adduct formation in cultured human liver slices and in assays for gene mutations (bacterial or mammalian cells in vitro) and gave equivocal results in assays for chromosomal damage (clastogenic effects were not consistently seen and occurred at high doses).

The genotoxic potential of levonorgestrel has not been fully investigated, although limited data available to date suggest that it does not appear to be genotoxic.
Use in Pregnancy (Category B3)

Microgynon 20 ED is contraindicated during pregnancy. If pregnancy occurs during treatment with Microgynon 20 ED, further intake must be stopped immediately.

Epidemiological studies have found no significant effects on foetal development in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

Use in Lactation

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk. Therefore, the use of COCs should generally not be recommended until the nursing mother has completely weaned her child.

Use in Children

Microgynon 20 ED is only indicated after menarche.

Use in the Elderly

Microgynon 20 ED is not indicated after menopause.

Patients with Hepatic Impairment

Microgynon 20 ED is contraindicated in women with severe hepatic disease as long as liver function values have not returned to normal (see CONTRAINDICATIONS).

Patients with Renal Impairment

Microgynon 20 ED has not been specifically studied in renally impaired patients.

Effect on Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

INTERACTIONS WITH OTHER MEDICINES

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

Effects of Other Medicines on Microgynon 20 ED

Interactions can occur with medicines that induce microsomal enzymes (e.g. cytochrome P450 enzymes, CYP34A), which can result in increased clearance of sex hormones and may lead to breakthrough bleeding and/or oral 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 prescribed any of these medicines 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 medicine administration and for 28 days after their discontinuation. If the period in which the barrier method is used runs beyond the end of the pink active tablets in the COC pack, the white placebo tablets should be omitted and the next COC pack started.

Women taking interacting medications on a chronic basis should consider another method of contraception.

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

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and herbal medicines containing St John’s Wort (*Hypericum perforatum*).

- **Substances with variable effects on the clearance of COCs**

When co-administered with COCs, many human immunodeficiency virus (HIV)/hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentration of oestrogen or progestogen. These changes may be clinically relevant in some cases.

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

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

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

**Influence of Microgynon 20 ED on Other Medicines**

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

*In vitro*, ethinyloestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical studies, administration of a hormonal contraceptive containing ethinyloestradiol lead to no, or a weak increase in CYP3A4 substrates (e.g. midazolam) and a weak (e.g. theophylline) to moderate (e.g. melatonin, tizanidine) increase of CYP1A2 substrates.

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

ADVERSE EFFECTS

Various adverse reactions have been associated with oral contraceptive use. The most commonly reported adverse reactions with Microgynon 20 ED are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain and breast tenderness. They occur in ≥ 1% of users.

Serious adverse reactions are arterial and venous thromboembolism.

The most serious reactions associated with the use of oral contraceptives are discussed under PRECAUTIONS.

In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide on whether COC use should be discontinued.

Clinical Trial Data

The table below displays the adverse events reported amongst patients in a clinical trial of Microgynon 20 for contraception (n = 805). It includes all adverse events reported with an incidence of 1% or greater. A total of 8.4% of women discontinued Microgynon 20 therapy due to the adverse events. Intermenstrual bleeding and metrorrhagia (4%) were the study events most frequently reported as the reason for discontinuing Microgynon 20 therapy. All other events that resulted in discontinuation were reported by less than 1% of the women.

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>Number of women affected</th>
<th>Percent of women affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>63</td>
<td>7.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>31</td>
<td>3.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>BODY AS A WHOLE</strong></td>
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<td></td>
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<tr>
<td>Flu Syndrome</td>
<td>9</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>NEUROLOGICAL</strong></td>
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<tr>
<td>Headache</td>
<td>142</td>
<td>17.6</td>
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<tr>
<td>Decreased libido</td>
<td>58</td>
<td>7.2</td>
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<tr>
<td>Migraine</td>
<td>47</td>
<td>5.8</td>
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<tr>
<td>Dizziness</td>
<td>40</td>
<td>5.0</td>
</tr>
<tr>
<td>Increased libido</td>
<td>29</td>
<td>3.6</td>
</tr>
<tr>
<td>Depression</td>
<td>22</td>
<td>2.7</td>
</tr>
<tr>
<td>Nervousness</td>
<td>17</td>
<td>2.1</td>
</tr>
<tr>
<td>ADVERSE EVENT</td>
<td>Number of women affected</td>
<td>Percent of women affected</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td><strong>REPRODUCTIVE</strong></td>
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<tr>
<td>Breast pain</td>
<td>90</td>
<td>11.2</td>
</tr>
<tr>
<td>Intermenstrual bleeding/metrorrhagia</td>
<td>35</td>
<td>4.3</td>
</tr>
<tr>
<td>Breast tension</td>
<td>11</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>SKIN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>62</td>
<td>7.7</td>
</tr>
</tbody>
</table>

A bioavailability study (n = 22) reported the following adverse events with a frequency of > 1%; intermenstrual bleeding 45%, headache/migraine 27%, dysmenorrhoea 23%, flu syndrome 18%, nausea 14%. A pharmacokinetic study (n = 18) reported the following adverse events with a frequency of > 1%; headache 78%, dysmenorrhoea 61%, flu syndrome 33%, common cold 28%, breast pain 17%.

**Post-Marking Data**

The following adverse events have been reported in users of low dose oral contraceptives and have been observed at the frequencies listed below, but an association has neither been confirmed nor totally refuted:

- **Very common**: ≥ 1 in 10 (≥ 10%)
- **Common**: ≥ 1 in 100 and < 1 in 10 (between 1% and 10%)
- **Uncommon**: ≥ 1 in 1000 and < 1 in 100 (between 0.1% and 1%)
- **Rare**: ≥ 1 in 10000 and < 1 in 1000 (between 0.01% and 0.1%)
- **Very rare**: < 1 in 10000 (< 0.01%)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Vaginitis (candidiasis)</td>
<td></td>
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<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td>Venous and arterial thromboembolic events ****</td>
<td></td>
<td>Aggravation of varicose veins</td>
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<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, abdominal pain</td>
<td>Abdominal cramps, bloating, diarrhoea</td>
<td></td>
<td>Pancreatitis, hepatic adenomas, hepatocellular carcinomas</td>
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<tr>
<td>Hepatobiliary</td>
<td></td>
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<td></td>
<td>Cholestatic jaundice</td>
<td>Gallbladder disease (including gallstones*)</td>
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<tr>
<td>Metabolism/nutrition</td>
<td></td>
<td></td>
<td>Changes in appetite (increase or decrease)</td>
<td>Glucose intolerance</td>
<td>Exacerbation of porphyria</td>
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<tr>
<td>Psychiatric</td>
<td>Mood changes including depression, changes in libido</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Very Common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>--------------------</td>
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</tr>
<tr>
<td>Nervous</td>
<td>Headache including migraines</td>
<td>Nervousness, dizziness</td>
<td>Rash, urticaria, chloasma (melasma) which may persist, hirsutism, alopecia</td>
<td>Erythema nodosum, erythema multiforme</td>
<td>Exacerbation of chorea</td>
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<tr>
<td>Skin and subcutaneous tissue</td>
<td>Acne</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td></td>
<td></td>
<td>Intolerance to contact lenses</td>
<td>Optic neuritis***, retinal vascular thrombosis</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast</td>
<td>Metrorrhagia (breakthrough bleeding and spotting)</td>
<td>Breast pain, tenderness, enlargement, secretion, dysmenorrhoea, change in menstrual flow, change in cervical ectropion and secretion, vaginitis, amenorrhoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary</td>
<td></td>
<td></td>
<td></td>
<td>Haemolytic uraemic syndrome</td>
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<tr>
<td>Immune</td>
<td></td>
<td></td>
<td>Anaphylactoid reactions including very rare cases of urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms</td>
<td></td>
<td>Exacerbation of systemic lupus erythematosus</td>
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<tr>
<td>General and administration site reactions</td>
<td>Fluid retention/oedema</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Investigations</td>
<td>Changes in weight (increase or decrease)</td>
<td>Increase in blood pressure, changes in serum lipid levels, including hypertriglyceridaemia</td>
<td></td>
<td>Decrease in serum folate levels**</td>
<td></td>
</tr>
</tbody>
</table>

* Oral contraceptives may worsen existing gall bladder disease and may accelerate the development of this disease in previously asymptomatic women
** Serum folate levels may be depressed by oral contraceptive therapy
*** Optic neuritis may lead to partial or complete loss of vision
Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives. ‘Venous and arterial thromboembolic events’ summarises the following Medical Entities: Peripheral deep venous occlusion, thrombosis and embolism/Pulmonary vascular occlusion, thrombosis, embolism and infarction/Myocardial infarction/Cerebral infarction and stroke not specified as haemorrhagic.

In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.

**DOSAGE AND ADMINISTRATION**

**How to Take Microgynon 20 ED**

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

One tablet is to be taken daily. The tablets must be taken in the order directed on the package at about the same time each day, with some liquid as needed. Daily tablet taking should be continuous for 28 consecutive days, starting with a pink active tablet marked with the corresponding day of the week from the green area of the Microgynon 20 ED pack. Each subsequent pack is to be started the day after the last tablet of the previous pack. A withdrawal bleed usually starts on day 2 to 3 after starting the white placebo tablets (last row) and may not have finished before the next pack is started.

**How to Start Microgynon 20 ED**

- No preceding hormonal contraceptive use (in the past month)

Tablet-taking has to start on day 1 of the woman’s natural cycle (i.e. the first day of her menstrual bleeding). If started on day 1 in this way, protection against pregnancy is immediate and no additional method of contraception is required. Starting on day 2 – 5 of the menstrual cycle is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

**When Changing Pills**

- Changing from a combined hormonal contraceptive (COC) or vaginal ring

The woman should start with Microgynon 20 ED preferably on the day after her last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet free or placebo tablet interval of her previous COC.

In case a vaginal ring has been used, the woman should start taking Microgynon 20 ED preferably on the day of removal, but at the latest when the next application would have been due.

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

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

- **Following first-trimester abortion**

The woman may start tablet-taking immediately. When doing so, she does not need additional contraceptive measures.

- **Following delivery or second-trimester abortion**

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

For breastfeeding women see Use in Lactation under PRECAUTIONS.

**Additional Contraceptive Precautions**

When additional contraceptive precautions are required the woman should be advised either to abstain from sex, or to use a barrier method of contraception, such as a cap (or diaphragm) plus spermicide, or for her partner to use a condom. Rhythm methods should not be advised as the COC disrupts the cyclical changes associated with the natural menstrual cycle, e.g. changes in temperature and cervical mucus.

**How to Shift Periods or How to Delay a Period**

To delay a period the woman should continue with another pack of Microgynon 20 ED by missing the white placebo tablets (last row) from her current pack. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of Microgynon 20 ED is then resumed after the usual 7-day placebo tablet interval.

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

**How to Manage Reduced Reliability**

When Microgynon 20 ED is taken according to the directions for use, the occurrence of pregnancy is highly unlikely. However, the reliability of COCs may be reduced under the following circumstances:

- **Management of missed tablets**

Missed pills from the last row of the blister are placebo tablets and thus can be disregarded. However they should be discarded to avoid unintentionally prolonging the placebo tablet phase. **The following advice only refers to missed pink active tablets (rows 1 – 3 of the blister)**:
If the woman is **less than 12 hours late** in taking any pink active tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If the woman is **more than 12 hours late** in taking any pink active tablet, contraceptive protection may be reduced. The more pink active tablets missed and the closer they are to the white placebo tablet phase the higher the risk of a pregnancy. The management of missed tablets can be guided by the following two basic rules:

1. ‘Active tablet’-taking must never be discontinued for longer than 7 days.
2. Seven days of uninterrupted ‘active tablet’-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

**Accordingly the following advice can be given in daily practice:**

**Week 1 of active tablets**

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

**Week 2 of active tablets**

The woman should take the last missed pink active tablet as soon as she remembers, even if this means taking two pink active tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed pink active tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than one pink active tablet, the woman should be advised to use extra precautions for 7 days.

**Week 3 of active tablets**

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

1. The woman should take the last missed pink active tablet as soon as she remembers, even if this means taking two pink active tablets at the same time. She then continues to take tablets at her usual time until all the pink active tablets are taken. The 7 white placebo tablets from the last row must be discarded. The next pack must be started right away. The woman is unlikely to have a withdrawal bleed until the end of the active tablets of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. The woman may also be advised to discontinue tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the hormone-free white-coated tablet phase, the possibility of a pregnancy should be considered.
• **Advice in case of gastrointestinal disturbances**

In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3 – 4 hours after tablet-taking, the advice concerning missed tablets, as given previously, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

**OVERDOSAGE**

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

**PRESENTATION AND STORAGE CONDITIONS**

Carton containing memo packs of 1 x 28 tablets, 2 x 28 tablets, 3 x 28 tablets or 4 x 28 tablets. Not all pack sizes may be marketed.

Each blister contains 21 small round pink active tablets, each containing ethinyloestradiol 20 µg and levonorgestrel 100 µg, followed by 7 large round white placebo tablets.

Store below 25°C.

**NAME AND ADDRESS OF THE SPONSOR**

Bayer Australia Ltd  
ABN 22 000 138 714  
875 Pacific Highway  
Pymble NSW 2073

**POISON SCHEDULE OF THE MEDICINE**

S4, PRESCRIPTION ONLY MEDICINE

**DATE OF FIRST INCLUSION IN THE ARTG**

16 November 1998

**DATE OF MOST RECENT AMENDMENT**

15 February 2017

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REFERENCES
