1. **NAME OF THE MEDICINAL PRODUCT**

Gynera 0.03 mg / 0.075 mg coated tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

21 hormone-containing white coated tablets:
Each coated tablet contains 0.03 mg ethinylestradiol, 0.075 mg gestodene

Excipient: lactose 36 mg

For a full list of excipients, see ‘Pharmaceutical Particulars’

3. **PHARMACEUTICAL FORM**

Coated tablet

4. **CLINICAL PARTICULARS**

4.1 **Indication(s)**

Oral contraception.

4.2 **Dosage and method of administration**

**Method of administration**

Oral use

**Dosage regimen**

**How to take Gynera**

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

Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. One tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after a 7-day tablet-free interval.

**How to start Gynera**

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

**Advice in case of gastro-intestinal disturbances**

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

If vomiting occurs within 3-4 hours after tablet-taking, the advice concerning missed tablets.

(1) Please also pay attention to the special notes described in the prescribing information of Diane-35.
Additional information on special populations

Children and adolescents
Gynera is only indicated after menarche.

Geriatric patients
Not available. Gynera is not indicated after menopause.

Patients with hepatic impairment
Gynera is contraindicated in women with severe hepatic diseases. See also section ‘Contraindications’.

Patients with renal impairment
Gynera has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

4.3 Contraindications

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

- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident.
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see under "Special Warnings and Special Precautions for Use".
- Sickle-cell anemia.
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Severe hepatic disease as long as liver function values have not returned to normal.
- History of deterioration of otosclerosis during pregnancy.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings and precautions for use

Warnings
Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents. These events occur rarely.
The risk of VTE is highest during the first year of use. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

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

VTE may be fatal (in 1-2 % of the cases).

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

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

Symptoms of deep venous thrombosis (DVT) can include: unilateral swelling of the leg or along a vein in the leg; pain or tenderness in the leg which may be felt only when standing or walking, increased warmth in the affected leg; red or discolored skin on the leg.

Symptoms of pulmonary embolism (PE) can include: sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may bring up blood; sharp chest pain which may increase with deep breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. Some of these symptoms (e.g. “shortness of breath”, “coughing”) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

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

Symptoms of MI can include: pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

Arterial thromboembolic events may be fatal.

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

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

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

The increased risk of thromboembolism in the puerperium must be considered (for information on pregnancy and lactation see section ‘Pregnancy and lactation’).

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

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

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

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low-dose COCs (<0.05 mg ethinylestradiol).

- Tumours

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

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.
In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal hemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.

- **Other conditions**

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

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

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

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

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing < 0.05 mg ethinylestradiol). However, diabetic women should be carefully observed while taking COCs.

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

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

Each coated tablet of this medicinal product contains 37.430 mg lactose monohydrate per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

Reasons for stopping oral contraception immediately:

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 thrombophlebitis or thromboembolic symptoms (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. Six 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. Increase in epileptic seizures.
7. Significant rise in blood pressure.
8. Onset of severe depression.
9. Severe upper abdominal pain or liver enlargement.
10. Clear exacerbation of conditions known to be capable of deteriorating during oral contraception or pregnancy.
11. Pregnancy is a reason for stopping immediately because it has been suggested by some investigations that oral contraceptives taken in early pregnancy may slightly increase the risk of foetal malformations. Other investigations have failed to support these findings. The possibility therefore cannot be excluded, but it is certain that if a risk exists at all, it is very small.

Medical Examination/consultation

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

Assessment of women prior to starting oral contraceptives (and at regular intervals thereafter) should include a personal and family medical history of each woman. Physical examination should be guided by this and by the contraindications and warnings for this product. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and, if judged appropriate by the clinician, breast, abdominal and pelvic examination including cervical cytology.

The following conditions require strict medical supervision during medication with oral contraceptives. Deterioration or first appearance of any of these conditions may indicate that use of the oral contraceptive should be discontinued:
Diabetes mellitus, or a tendency towards diabetes mellitus (e.g. unexplained glycosuria), hypertension, varicose veins, a history of phlebitis, otosclerosis, multiple sclerosis, epilepsy, porphyria, tetany, disturbed liver function, Sydenham's chorea, renal dysfunction, family history of clotting disorders (see also contraindications), obesity, family history of breast cancer and patient history of benign breast disease, history of clinical depression, systemic lupus erythematosus, uterine fibroids, an intolerance of contact lenses, migraine, gall-stones, cardiovascular diseases, chloasma, asthma, or any disease that is prone to worsen during pregnancy.
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.

Reduced efficacy
The efficacy of COCs may be reduced in the event of e.g. missed tablets, gastro-intestinal disturbances (section ‘Advice in case of gastro-intestinal disturbances’) during tablet taking or concomitant medication (section "Interaction with other medicinal products and other forms of interaction").

Reduced cycle control
With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use.
In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions described in Section "Dosage and method of administration", it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicaments on Gynera

Interactions of other drugs (enzyme inducers, some antibiotics) with oral contraceptives may lead to breakthrough bleeding and/or contraceptive failure. Women on treatment with any of these drugs should temporarily use a barrier method in addition to the COC or choose another method of contraception. With microsomal enzyme-inducing drugs, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after discontinuation. If the period during which the barrier method is used runs beyond the end of the tablets in the COC pack, the next COC pack should be started without the usual tablet-free interval.

Paragraphs proposed to be changed from optional (as in current xCCDS) to mandatory.

Substances diminishing the efficacy of COCs (enzyme-inducers and antibiotics)

- **Enzyme induction (increase of hepatic metabolism):** Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John’s wort).

  Also HIV protease (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and combinations of them, have been reported to potentially increase hepatic metabolism.

- **Antibiotics (interference with enterohepatic circulation):** Some clinical reports suggest that enterohepatic circulation of estrogens may decrease when certain antibiotic agents are given, which may reduce ethinylestradiol concentrations (e.g. penicillins, tetracyclines).

Effects of COCs on other medicaments

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

Other forms of interactions

- **Laboratory tests**

  The use of contraceptive steroids may influence the results of certain laboratory tests.
4.6 Pregnancy and lactation

**Pregnancy**

Gynera is not indicated during pregnancy. If pregnancy occurs during treatment with Gynera, further intake must be stopped. However, extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

**Lactation**

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

4.7 Effects on ability to drive or use machines

No observed effects.

4.8 Undesirable effects

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common (≥ 1/100)</th>
<th>Uncommon (≥ 1/1000 and &lt; 1/100)</th>
<th>Rare (&lt;1/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td>contact lens intolerance</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>nausea, abdominal pain</td>
<td>vomiting, diarrhea</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>hypersensitivity</td>
</tr>
<tr>
<td>Investigations</td>
<td>weight increased</td>
<td></td>
<td>weight decreased</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>fluid retention</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache</td>
<td>migraine</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>depressed mood, mood altered</td>
<td>libido decreased</td>
<td>libido increased</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>breast pain, breast tenderness</td>
<td>breast hypertrophy</td>
<td>vaginal discharge, breast discharge</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash, urticaria</td>
<td></td>
<td>Erythema nodosum, erythema multiforme</td>
</tr>
</tbody>
</table>

The following serious adverse events have been reported in women using COCs, which are discussed in section ‘Special warnings and precautions for use’:
- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Cerebrovascular accidents
- Hypertension
-9-

- Hypertriglyceridemia
- Changes in glucose tolerance or effect on peripheral insulin resistance
- Liver tumours (benign and malignant)
- Liver function disturbances
- Chloasma
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham’s chorea; herpes gestationis; otosclerosis-related hearing loss, Crohn’s disease, ulcerative colitis, cervical cancer

The frequency of diagnosis of breast cancer is very slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see sections ‘Contraindications’ and ‘Special warnings and precautions for use’.

4.9 Overdose
There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

5.2 Pharmacokinetic properties
- Gestodene

Absorption
Orally administered gestodene is rapidly and completely absorbed. Peak serum concentrations of 4ng/ml are reached at about 1 hour after single ingestion. Bioavailability is about 99%.

Distribution
Gestodene is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1-2% of the total serum drug concentrations are present as free steroid, 50-70% are specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the proportion of gestodene bound to the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of gestodene is 0.7 l/kg.

Metabolism
Gestodene is completely metabolized by the known pathways of steroid metabolism. The clearance rate from serum is 0.8 ml/min/kg. When gestodene was acutely co-administered with ethinylestradiol, no direct interaction was found.

Elimination
Gestodene serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of 12-15 hours. Gestodene is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 6:4. The half-life of metabolite excretion is about 1 day.

Steady-state conditions
Gestodene pharmacokinetics are influenced by SHBG levels, which are increased threefold when co-administered with ethinylestradiol. Following daily ingestion drug serum levels increase about fourfold reaching steady-state conditions during the second half of a treatment cycle.

- Ethinylestradiol

Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 80 pg/ml are reached within 1-2 hours. During absorption and first-liver passage, ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of about 45% with a large interindividual variation of about 20-65%.

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

Metabolism
Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The clearance rate was reported to be 2.3- 7ml/min/kg.

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

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 ethinylestradiol will be reached after about one week.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Maize starch
Povidone 25000
Sodium calcium edetate
Magnesium stearate
Sucrose
Povidone 700000
Macrogol 6000
Calcium carbonate
Talc
Montanlycol wax

6.2 Incompatibilities
None

6.3 Shelf life
5 years

6.4 Special precautions for storage
Not above 25°C

6.5 Nature and contents of container
Gynera tablets are supplied in memo-packs of 21 tablets, 3 x 21 tablets, 6 x 21 tablets.

MANUFACTURE:
Bayer Schering Pharma AG, Berlin, Germany