## Core Safety Profile

<table>
<thead>
<tr>
<th>Active substance:</th>
<th>Ethinylestradiol + Gestodene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical form(s)/strength:</td>
<td>Tablet</td>
</tr>
<tr>
<td>P-RMS:</td>
<td>FR/H/PSUR/0058/001</td>
</tr>
<tr>
<td>Date of FAR:</td>
<td>16.12.2009</td>
</tr>
</tbody>
</table>
4.3 Contraindications

Combined Oral Contraceptives must not be used in women with any of the following conditions:

- Deep vein thrombosis (current or history)
- Thromboembolism (current or history)
- Cerebrovascular or coronary artery disease
- Thrombogenic valvulopathies
- Thrombogenic rhythm disorders
- Hereditary or acquired disposition for venous or arterial thrombosis
- Headache with focal neurological symptoms, such as aura
- Diabetes with vascular involvement
- Uncontrolled hypertension
- Current or previous pancreatitis if associated with serious hypertriglyceridemia
- Known or suspected carcinoma of the breast, or other known or suspected estrogen dependent neoplasia
- Hepatic adenomas or carcinomas, or active liver disease, as long as liver function has not returned to normal
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy (see section 4.6)
- Hypersensitivity to any of the components of /...

4.4 Special warnings and precautions for use

Warnings

Cigarette smoking increases the risk of serious cardiovascular adverse reactions from COC use. This risk increases with age and with the extent of smoking and is quite marked in women over 35 years of age. Women who use COCs should be strongly advised not to smoke.

Venous and arterial thrombosis and thromboembolism

Use of COCs is associated with an increased risk of venous and arterial thrombotic and thromboembolic events. For any particular estrogen/progestin combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestin that is compatible with a low failure rate and the needs of the individual patient.

- Venous thrombosis and thromboembolism

Use of COCs increases the risk of venous thrombotic and thromboembolic events. The use of any COC carries an increased risk of venous thrombotic and thromboembolic events, such as deep venous thrombosis and pulmonary embolism, compared with no use. The excess risk is highest during the first year a women ever uses a combined oral contraceptive. This increased risk is less than the risk of venous thrombotic and thromboembolic events associated with pregnancy which is estimated as 60 cases per 100,000 pregnant women years. Venous thromboembolism is fatal in 1-2% of cases.

In several epidemiological studies it has been found that women using COCs with ethinyl estradiol, mostly with a dose of 30 µg, and a progestin such as gestodene have an increased risk of venous thrombotic and thromboembolic events compared with those using COCs containing less than 50 µg of ethinyl estradiol and the progestin levonorgestrel. Data from some additional studies have not shown this increase in risk.
For COCs containing 30 µg of ethinyl estradiol combined with desogestrel or gestodene compared with those containing less than 50 µg of ethinyl estradiol and levonorgestrel, the overall relative risk of venous thrombotic and thromboembolic events has been estimated to range between 1.5 and 2.0. The incidence of venous thrombotic and thromboembolic events for levonorgestrel containing COCs with less than 50 µg of ethinyl estradiol is approximately 20 cases per 100,000 women-years of use. For COCs containing gestodene or desogestrel, the incidence is approximately 30-40 cases per 100,000 women-years of use, i.e. additional 10-20 cases per 100,000 women-years of use. This compares with 5 to 10 cases per 100,000 women-years for non-users.

The risk of venous thrombotic and thromboembolic events is further increased in women with conditions predisposing for venous thrombosis and thromboembolism.

Examples of predisposing conditions for venous thrombosis and thromboembolism are:
- obesity
- surgery or trauma with increased risk of thrombosis
- recent delivery or second-trimester abortion
- prolonged immobilization
- increasing age

If feasible, COCs should be discontinued:
- for four weeks prior to and for two weeks after complete recovery after elective surgery that poses an increased risk of thrombosis, and
- during prolonged immobilization.

Since the immediate post-partum period is associated with an increased risk of thromboembolism, COCs should be started no earlier than day 28 after delivery or second-trimester abortion.

- **Arterial thrombosis and thromboembolism**

The use of COCs increases the risk of arterial thrombotic and thromboembolic events. Reported events include myocardial infarction and cerebrovascular events (ischemic and hemorrhagic stroke, transient ischemic attack).

The risk of arterial thrombotic and thromboembolic events is further increased in women with underlying risk factors.

Caution must be exercised when prescribing COCs for women with risk factors for arterial thrombotic and thromboembolic events.

Examples of risk factors for arterial thrombotic and thromboembolic events are:
- smoking
- hypertension
- hyperlipidemias
- obesity
- increasing age

COC users with migraine (particularly migraine with aura) may be at increased risk of stroke (see section 4.3).
**Ocular lesions**
With use of COCs, there have been reports of retinal vascular thrombosis, which may lead to partial or complete loss of vision. If there are signs or symptoms such as visual changes, onset of proptosis or diplopia, papilledema, or retinal vascular lesions, the COC should be discontinued and the cause immediately evaluated.

**Blood pressure**
Increases in blood pressure have been reported in women taking COCs.

In women with hypertension, a history of hypertension or hypertension related diseases, another method of contraception may be preferable. If COCs are used in such cases, close monitoring is recommended and, if a significant increase in blood pressure occurs, COCs should be discontinued.

COC use is contraindicated in women with uncontrolled hypertension (see section 4.3).

**Carcinoma of the reproductive organs**

**Cervical cancer**
The most important risk factor for cervical cancer is persistent human papillomavirus infection.

Some studies suggest that COC use may be associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In cases of undiagnosed abnormal genital bleeding, adequate diagnostic measures are indicated.

**Breast cancer**
Established risk factors for the development of breast cancer include increasing age, family history, obesity, nulliparity, and late age for first full-term pregnancy.

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 using COCs compared to never-users. The increased 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 lifetime risk of breast cancer.

**Hepatic neoplasia/ Liver disease**
In very rare cases, hepatic adenomas, and in extremely rare cases, hepatocellular carcinoma may be associated with COC use. The risk appears to increase with duration of COC use. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Women with a history of COC-related cholestasis or women with cholestasis during pregnancy are more likely to have this condition with COC use. If these patients receive a COC they should be carefully monitored and, if the condition recurs, the COC should be discontinued.

Hepatocellular injury has been reported with COC use. Early identification of drug-related hepatocellular injury can decrease the severity of hepatotoxicity when the drug is discontinued. If hepatocellular injury is diagnosed, patients should stop their COC, use a non-hormonal form of contraception and consult their doctor.
Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until liver function has returned to normal.

**Migraine/Headache**
The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent or severe requires discontinuation of COCs and evaluation of the cause.

Women with migraine (particularly migraine with aura) who take COCs may be at increased risk of stroke (see section 4.3).

**Immune**

**Angioedema**
Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema.

**PRECAUTIONS**

**Medical examinations**
A complete personal and family medical history and physical examination, including blood pressure, should be taken prior to the initiation of COC use.

Before COC use is initiated, a thorough individual history, family history, and physical examination, including a blood pressure determination, should be performed. An examination of the breasts, liver, extremities, and pelvic organs should also be conducted. A Papanicolaou (Pap) smear should be performed if the patient has been sexually active or if it is otherwise indicated.

Such medical examinations should be repeated at least annually during the use of COCs.

The first follow-up visit should occur 3 months after COCs are prescribed. At each annual visit, examination should include those procedures that were performed at the initial visit, as described previously.

**Carbohydrate and lipid effects**
Glucose intolerance has been reported in COC users. Women with impaired glucose tolerance or diabetes mellitus who use COCs should be carefully monitored.

A small proportion of women will have adverse lipid changes while taking OCs. Nonhormonal contraception should be considered in women with uncontrolled dyslipidemias. Persistent hypertriglyceridemia may occur in a small proportion of COC users. Elevations of plasma triglycerides may lead to pancreatitis and other complications.

Women who are being treated for hyperlipidemias should be followed closely if they elect to use COCs.

**Genital bleeding**
In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has not been taken according to directions prior to the first missed withdrawal bleed, or if two consecutive withdrawal bleeds are missed, tablet-taking should be discontinued and a non hormonal back-up method of contraception should be used until the possibility of pregnancy is excluded.
Breakthrough bleeding/spotting may occur in women taking COCs, especially during the first three months of use. If this bleeding persists or recurs, non hormonal causes should be considered and adequate diagnostic measures may be indicated. If pathology has been excluded, continued use of the COC or a change to another formulation may solve the problem.

Some women may encounter post-pill amenorrhea (possibly with anovulation) or oligomenorrhea, especially when such a condition was preexistent.

**Depression**

Women with a history of depression who use COCs should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking COCs should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related.

**Other**

Patients should be counseled that this product does not protect against HIV infection (AIDS) or other sexually transmitted diseases.

Diarrhea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations (see section 4.2 and 4.5).

... contains lactose. Should not be used by patients with hereditary galactose intolerance, a specific form of hereditary lactase deficiency (Lapp Lactase deficiency) or glucose/galactose malabsorption.

... also contains saccarose. Should not be used by patients with hereditary fructose intolerance, glucose/galactose malabsorption and sucrase-isomaltase deficiency.

### 4.5 Interaction with other medicinal products and other forms of interaction

Interactions between ethinyl estradiol (EE) and other substances may lead to decreased or increased serum EE concentrations, respectively.

Decreased EE serum concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the COC.

During concomitant use of EE-containing products and substances that may lead to decreased EE serum concentrations, it is recommended that a nonhormonal back-up method of birth control (such as condoms and spermicide) be used in addition to the regular intake of ... In the case of prolonged use of such substances COCs should not be considered the primary contraceptive.

After discontinuation of substances that may lead to decreased EE serum concentrations, use of a nonhormonal back-up method is recommended for at least 7 days. Longer use of a back-up method is advisable after discontinuation of substances that have lead to induction of hepatic microsomal enzymes, resulting in decreased EE serum concentrations. It may sometimes take several weeks until enzyme induction has completely subsided, depending on dosage, duration of use and rate of elimination of the inducing substance.
Examples of substances that may decrease serum EE concentrations:

- Any substance that reduces gastrointestinal transit time
- Substances that induce hepatic microsomal enzymes, such as rifampicin, rifabutin, barbiturates, primidone, carbamazepin, phenylbutazone, phenytoin, dexamethasone, griseofulvin, topiramate, some protease inhibitors, modafinil and possibly also oxcarbazepin, felbamat, ritonavir and nevirapin
- Hypericum perforatum, also known as St. John’s wort (possibly by induction of hepatic microsomal enzymes)
- Certain antibiotics (e.g., penicillins, tetracyclines), by a decrease of enterohepatic circulation of estrogens.

Examples of substances that may increase serum EE concentrations:

- Atorvastatin
- Competitive inhibitors for sulfation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and paracetamol
- Substances that inhibit cytochrome P 450 3A4 isoenzymes such as indinavir, fluconazole, voriconazole and troleandomycin.

Troleandomycin may increase the risk of intrahepatic cholestasis during coadministration with COCs.

EE may interfere with the metabolism of other drugs by inhibiting hepatic microsomal enzymes, or by inducing hepatic drug conjugation, particularly glucuronidation or by other mechanisms. Accordingly, plasma and tissue concentrations may either be increased (e.g. cyclosporine, theophylline, corticosteroids) or decreased (e.g. lamotrigine, levothyroxin, valproat).

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

**Effects on laboratory parameters**

The use of COCs may cause certain physiologic changes that may be reflected in the results of certain laboratory tests, including:

- biochemical parameters of liver function (including a decrease in bilirubin and alkaline phosphatase), thyroid function (increased total T3 and T4 due to increased TBG, decreased free T3 resin uptake), adrenal function (increased plasma cortisol, increased cortisol binding globulin, decreased dehydroepiandrosterone sulfate (DHEAS), and renal function (increased plasma creatinine and creatinine clearance)
- plasma levels of (carrier) proteins, such as corticosteroid-binding globulin and lipid/lipoprotein fractions
- parameters of carbohydrate metabolism
- parameters of coagulation and fibrinolysis
- decreased serum folate levels
4.6 Pregnancy and lactation

Pregnancy

If pregnancy occurs during treatment with COCs, further intake should be discontinued. There is no conclusive evidence that the estrogen and progestin contained in the COC will damage the developing child if conception accidently occurs during COC use. See section 4.3.

Lactation

Small amounts of contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk.

The use of COCs is generally not recommended until the nursing mother has completely weaned her child.

4.7 Effects on ability to drive and use machine

/.../ has not been studied in relation to the effects on the ability to drive or use machines.

4.8 Undesirable effects

Use of COCs has been associated with:

- an increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischemic attack, venous thrombosis and pulmonary embolism
- an increased risk of cervical intraepithelial neoplasia and cervical cancer
- an increased risk of being diagnosed with breast cancer
- an increased risk of benign hepatic tumors (eg. focal nodular hyperplasia, hepatic adenoma)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestations</td>
<td></td>
</tr>
<tr>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Vaginitis, including candidiasis</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, and unspec</td>
<td></td>
</tr>
<tr>
<td>Very Rare (≤1/10.000)</td>
<td>Hepatocellular carcinomas</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Rare (≥1/10.000 to ≤1/1.000)</td>
<td>Anaphylactic/anaphylactoid reactions, including very rare cases of urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms</td>
</tr>
<tr>
<td>Disorder Type</td>
<td>Frequency</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon (≥1/1.000 to ≤1/100)</td>
<td></td>
</tr>
<tr>
<td>Rare (≥1/10.000 to ≤1/1.000)</td>
<td></td>
</tr>
<tr>
<td>Very Rare (≤1/10.000)</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
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<tr>
<td>Common (≥1/100 to &lt;1/10)</td>
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</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very Common (≥1/10)</td>
<td></td>
</tr>
<tr>
<td>Common (≥1/100 to &lt;1/10)</td>
<td></td>
</tr>
<tr>
<td>Very rare (≤1/10.000)</td>
<td></td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rare (≥1/10.000 to ≤1/1.000)</td>
<td></td>
</tr>
<tr>
<td>Very rare (≤1/10.000)</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very rare (≤1/10.000)</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
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</tr>
<tr>
<td>Common (≥1/100 to &lt;1/10)</td>
<td></td>
</tr>
<tr>
<td>Uncommon (≥1/1.000 to ≤1/100)</td>
<td></td>
</tr>
<tr>
<td>Very rare (≤1/10.000)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td><strong>Hepato-biliary disorder</strong></td>
<td></td>
</tr>
<tr>
<td>Rare (≥1/10.000 to ≤1/1.000)</td>
<td></td>
</tr>
<tr>
<td>Very rare (≤1/10.000)</td>
<td></td>
</tr>
<tr>
<td>Not known (cannot be estimated from the available data)</td>
<td></td>
</tr>
</tbody>
</table>
## Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Acne</td>
</tr>
<tr>
<td>Uncommon (≥1/1.000 to ≤1/100)</td>
<td>Rash, chloasma (melasma), which may persist, hirsutism, alopecia</td>
</tr>
<tr>
<td>Rare (≥1/10.000 to ≤1/1.000)</td>
<td>Erythema nodosum</td>
</tr>
<tr>
<td>Very rare (≤1/10.000)</td>
<td>Erythema multiforme</td>
</tr>
</tbody>
</table>

## Renal and urinary disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare (≤1/10.000)</td>
<td>Hemolytic uremic syndrome</td>
</tr>
</tbody>
</table>

## Reproductive system and breast disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥1/10)</td>
<td>Breakthrough bleeding/spotting</td>
</tr>
<tr>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Breast pain, tenderness, enlargement, secretion; dysmenorrhea; change in menstrual flow; change in cervical ectropion and secretion; amenorrhea</td>
</tr>
</tbody>
</table>

## General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Fluid retention/edema</td>
</tr>
</tbody>
</table>

## Investigations

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Changes in weight (increase or decrease)</td>
</tr>
<tr>
<td>Uncommon (≥1/1.000 to ≤1/100)</td>
<td>Increase in blood pressure; changes in serum lipid levels, including hypertriglyceridemia</td>
</tr>
<tr>
<td>Rare (≥1/10.000 to ≤1/1.000)</td>
<td>Decrease in serum folate levels***</td>
</tr>
</tbody>
</table>

* Optic neuritis may lead to partial or complete loss of vision.
** COCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.
*** Serum folate levels may be depressed by COC therapy. This may be of clinical significance if the woman becomes pregnant shortly after discontinuing COCs.

### 4.9 Overdose

Symptoms of oral contraceptive overdosage in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment of overdose, if necessary, is directed to the symptoms.