Ethinylestradiol/Levonorgestrel

Core Safety Profile

4.3 CONTRAINDICATIONS

Combined oral contraceptives (COCs) are not to 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 must be stopped immediately.

- Venous thrombosis present or in history (deep venous thrombosis, pulmonary embolism).
- Arterial thrombosis present or in history (e.g. myocardial infarction) or prodromal conditions (e.g. angina pectoris and transient ischaemic attack).
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- Cerebrovascular accident present or in history
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see section 4.4)
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- Severe hepatic disease, current or previous, as long as liver function values have not returned to normal.
- Presence or history of liver tumors (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substances levonorgestrel, ethinylestradiol or to any of the excipients Ehtinylestradiol/levonorgestrel tablets.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

<u>Warnings</u>

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

- *Circulatory Disorders*

Epidemiological studies have shown that the incidence of VTE in users of oral contraceptives with low oestrogen content (<50 µg ethinylestradiol) ranges from about 20 to 40 cases per 100,000 women-years, but this risk estimate varies according to the progestogen. This compares with 5 to 10 cases per 100,000 women-years for non-users. The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use.

The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2 % of the cases.

The overall absolute risk (incidence) of VTE for levonorgestrel containing combined oral contraceptives with 30 µg ethinylestradiol is approximately 20 cases per 100,000 women-years of use. Epidemiological studies have also associated the use of combined COCs with an increased risk for myocardial infarction, transient ischaemic attack and for stroke.

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

Symptoms of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident can include:

- unusual unilateral leg pain and/or swelling
- sudden severe pain in the chest, whether or not it radiates to the left arm
- sudden breathlessness
- sudden onset of coughing
- 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.

The risk for venous thromboembolic complications in COCs users increases with:

- increasing age
- a positive family history (venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.

- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue the pill (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.
- obesity (body mass index over 30 kg/m²).
- there is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The risk of arterial thromboembolic complications or of a cerebrovascular accident in COC users increases with:
- increasing age
- smoking (women over 35 years should be strongly advised not to smoke if they wish to use an COC)
- dyslipoproteinemia
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation

The increased risk of thromboembolism in the puerperium must be considered (see Section 4.6 Pregnancy and Lactation).

Other medical conditions which have been associated with adverse vascular events include diabetes mellitus, systemic lupus erythematosus, hemolytic uremic syndromeand 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).

- *Tumors*

An increased risk of cervical cancer in long-term users of COCs has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behavior and other factors such as human papilloma virus (HPV).

A meta-analysis of 54 epidemiological studies showed 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 tumors, and even more rarely, malignant liver tumors have been reported in users of COCs. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. A hepatic tumor 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. Only in these rare cases an immediate discontinuation of COC use is justified. If, during the use of a COC in preexisting hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. 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 during both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstones; 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 the liver function values return to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

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. However, diabetic women should be carefully monitored, particularly in the early stage of COC use.
Worsening of Crohn's disease and of ulcerative colitis has been reported during 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.

This medicinal product contains lactose. 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.

Medical examination/consultation
Prior to the initiation or reinstitution of Ehtinylestradiol/levonorgestrel a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed,, guided by the contraindications (see section 4.3 Contraindications) and warnings (see section 4.4 Special Warnings and special precautions for use'). The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman..

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

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

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 tablet-free interval. If the COC has been taken according to the directions described in section 4.2 Posology 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

- Interactions

Interactions between COCs and other drugs may impair the contraceptive efficacy and/or lead to breakthrough bleeding and/or contraceptive failure.

Women on treatment with any of these drugs should temporarily use a barrier method or another method of contraception in addition to the COC. With liver enzyme inducing drugs, the barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation.

Women on treatment with antibiotics (except rifampicin and griseofulvin) should use a barrier method during the use of the antibiotics and until 7 days after their discontinuation.
If the drug therapy runs beyond the end of
21 tablets: …the tablets in the COC pack, the next COC pack should be started without the usual tablet-free interval.
21+7 tablets: ...the hormone-containing <product> coated tablets in the COC pack, the hormone-free white coated tablets should be omitted and the next COC pack be started.

Hepatic metabolism: Interactions can occur with drugs that induce hepatic microsomal enzymes, resulting in increased clearance of sex hormones (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing the herbal remedy 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.

Eenterohepatic circulation: Some clinical reports suggest that enterohepatic circulation of estrogens may decrease when certain antibiotic agents (e.g. penicillins, tetracyclins)are given at the same time, which may reduce ethinylestradiol concentrations in serum.

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

Oral contraceptives may interfere with the metabolism of certain other drugs. Increased plasma concentrations of cyclosporin have been reported with concomitant administration of OCs. COCs have been shown to induce metabolism of lamotrigine resulting in sub-therapeutic plasma concentrations of lamotrigine.

- 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 blood coagulation and fibrinolysis. The changes generally remain within the normal laboratory range.

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

4.6 PREGNANCY AND LACTATION

Ehtinylestradiol/levonorgestrel is not indicated during pregnancy.
If the woman becomes pregnant while using Ehtinylestradiol/levonorgestrel tablets, 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 at unintentional intake of contraceptive pills in early pregnancy.

Lactation may be influenced by contraceptive pills as they may reduce the amount of breast milk and change its composition. Thus, the use of combined oral contraceptives should generally not be recommended until the nursing mother has weaned her child off breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted in breast milk. These amounts may affect the child.

4.7 EFFECTS ON ABILITY TO DRIVE OR USE MACHINES

Ehtinylestradiol/levonorgestrel has no effects or negligible influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

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

Organ system	**Common (≥ 1/100)**	**Uncommon (≥ 1/1000 and <1/100)**	**Rare (< 1/1000)**
Eye disorders			Contact lens intolerance
Gastrointestinal disorders	Nausea Abdominal pain	Vomiting Diarrhea	
Immune system disorders			Hypersensitivity
Investigations	Weight increased		Weight decreased
Metabolism and nutrition disorders		Fluid retention	
Nervous system disorders	Headache	Migraine	
Psychiatric disorders	Depressed mood Mood altered	Libido decreased	Libido increased
Reproductive system and breast disorders	Breast tenderness Breast pain,	Breast enlargement	Breast discharge Vaginal discharge
Skin and subcutaneous tissue disorders		Rash Urticaria	Erythema nodosum Erythema multiforme

The following serious adverse events have been reported in women using COCs, which are discussed in section 4.4 Special warnings and precautions for use:

- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Hypertension
- Liver tumours

- Crohn’s disease, ulcerative colitis, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice;

The frequency of diagnosis of breast cancer is 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 4.3 Contraindications and 4.4 Special warnings and precautions for use**.**

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

4.9 OVERDOSE

There have been no reports of serious effects from overdose. Symptoms that may be caused by overdose are nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and the treatment is symptomatic.