

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 during COC use, the product should be stopped immediately.

- Thrombophlebitis or thromboembolic disorders
- Presence or history of venous thrombosis (deep venous thrombosis, pulmonary embolism)
- Presence or history of arterial thrombosis (myocardial infarction, cerebrovascular accident) or prodromal conditions (e.g. transient ischaemic attack, angina pectoris).
- History of migraine with focal neurological symptoms
- Known predisposition for venous or arterial thrombosis, such as Activated Protein C (APC) resistance, antithrombin-III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid antibodies
- Valvular heart disease with complications
- Severe hypertension (persistent systolic values of ≥ 160 or persistent diastolic values of ≥ 100 mm Hg)
- Diabetes mellitus with vascular involvement.
- 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').
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected malignant conditions of the genital organs or the breasts, if sex steroid-influenced.
- Endometrial hyperplasia.
- Undiagnosed vaginal bleeding.
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Known or suspected pregnancy.
- Hypersensitivity to any of the active substances of Cilest or to any of the excipients.

4.4 Special warnings and special precautions for use

Warnings

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 woman 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 its use should be discontinued.

1. Circulatory disorders

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 cases.

The approximate occurrence of VTE in users of oral contraceptives with low oestrogen content (<50 µg ethinyl estradiol) is about 20 cases per 100 000 women-years compared to 5 to 10 cases per 100 000 women-years for non-users.

It is not known how Cilest influences the risk of VTE compared with other combined oral contraceptives.

Epidemiological studies have also associated the use of COCs with an increase risk for arterial thromboembolism.

The risk of venous thromboembolism increases with:

- increasing age;
- a positive family history (i.e. 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 hormonal contraceptive use;
- obesity (body mass index over 30 kg/m²)
- prolonged immobilisation, 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.
- and possibly also with superficial thrombophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the etiology of venous thromboembolism.

The risk of arterial thromboembolic complications increases with:

- increasing age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- dyslipoproteinaemia;
- obesity (body mass index over 30 kg/m²)
- hypertension;
- valvular heart disease;
- atrial fibrillation;
- a positive family history (i.e. arterial thrombosis 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 hormonal contraceptive use

If thromboembolic complication develops or is suspected, the treatment should be discontinued. The presence of one serious risk factor or multiple risk factors for venous or arterial disease, respectively, may also contribute a contraindication.

Symptoms of venous or arterial thrombosis can include: 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; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; 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.

The increased risk of thromboembolism in the puerperium must be considered (for information on 'Pregnancy and lactation' see Section 4.6).

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).

2. Tumours

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 behaviour and other factors such as human papilloma virus (HPV).

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 haemorrhages. A hepatic 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.

3. Other conditions

- Women with hypertriglyceridaemia, 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. A relationship between COC use and clinical hypertension has not been established. 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; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hear-loss.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. At least three months should elapse after liver function tests have returned to normal following any hepatitis before administration of a COC. 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 regimens in diabetics using COCs. 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.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

All this information should be taken into account when prescribing this COC. When counselling the choice of contraceptives method(s) all the above information should be taken into account.

Medical examination/consultation

Prior the initiation or reinstitution of Cilest a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contra-indications (section 4.3) and warnings (section 4.4). The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of further periodic checks should be based on established practice guidelines and be adapted to the individual woman.

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

Reduced efficacy

The efficacy of COCs may be reduced in the event of missed tablets (section 4.2), vomiting (section 4.2) or concomitant medication (section 4.5).

Herbal preparations containing St. John's wort (*Hypericum perforatum*) should not be used while taking Cilest due to the risk of decreased plasma concentrations and reduced clinical effects of Cilest (see section 4.5 Interactions).

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, 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

Drug interactions which result in an increased clearance of sex hormones can lead to breakthrough bleeding and oral contraceptive failure. This has been established with hydantoin, barbiturates, modafinil, phenytoin sodium, primidone, carbamazepine and rifampicin; oxcarbazepine, topiramate, felbamate, ritonavir, griseofulvin and bosentan are also suspected. The mechanism of this interaction appears to be based on the hepatic enzyme-

inducing properties of these drugs. Maximal enzyme induction is generally not seen for 2-3 weeks but may then be sustained for at least 4 weeks after the cessation of drug therapy. Contraceptive failures have also been reported with antibiotics, such as ampicillins and tetracyclines.

The mechanism of this effect has not been elucidated.

Women on short-term treatment with any of the above-mentioned classes of drugs or individual drugs should temporarily use a barrier method in addition to the COC, i.e. during the time of concomitant drug administration and for 7 days after their discontinuation. For women on rifampicin a barrier method should be used in addition to the COC during the time of rifampicin administration and for 28 days after its discontinuation.

If concomitant drug administration runs beyond the end of the tablets in the COC pack, the next COC pack should be started without the usual tablet-free interval.

In women on long-term treatment with hepatic enzyme-inducing drugs, experts have recommended to increase the contraceptive steroid doses.

If a high contraceptive dosage is not desirable or appears to be unsatisfactory or unreliable, e.g. in the case of irregular bleeding, another method of contraception should be advised.

Herbal preparations containing St. John's wort (*Hypericum perforatum*) should not be taken concomitantly with oral contraceptives as this could potentially lead to a loss of contraceptive effect.

Breakthrough bleeding and unintended pregnancies have been reported. This is due to induction of 24 drug metabolising enzymes by St. John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's wort.

Medications that are metabolized primarily by glucuronic acid conjugation (e.g. lamotrigine) may have significant increases in plasma clearance and therefore reduced efficacy when taken concomitantly with hormonal contraceptives.

Treatment with activated charcoal will compromise absorption of steroid hormones. Drugs that increase gastrointestinal motility, e.g. metoclopramid, may reduce hormone absorption.

The interactions described above primarily involve the estrogen component of Cilest, ethinyl estradiol. The progestin component, norgestimate, is rapidly hydrolyzed to norelgestromin, followed by biotransformation to norgestrel. The specific enzyme(s) catalyzing these reactions are not known. Therefore, interactions affecting their transformation cannot be predicted.

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.

Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

Note! The prescribing information of concomitant medications should be checked to identify potential interactions.

4.6 Pregnancy and lactation

Pregnancy

Cilest is contraindicated during pregnancy.

Epidemiological studies indicate no increased risk of congenital anomalies in children born to women who used oral contraceptives prior to pregnancy. The majority of recent epidemiological studies also do not indicate a teratogenic effect, when taken inadvertently during early pregnancy.

Lactation

Contraceptive steroids and/or their metabolites may be excreted in breast milk. In addition, combination hormonal contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use Cilest or other combination hormonal contraceptives but to use other forms of contraception until the child is fully weaned.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

The evaluation of the clinical safety of Cilest was based on three phase 3 studies conducted: a controlled 2-cell safety and comparison study (A-3437), a controlled 2-cell comparison study of coagulation effects (D83-001) and an open efficacy and safety study (C82-083). All 3 studies were two year (24 cycles) studies and cumulatively evaluated a total of 1647 women and 22,237 cycles. Information on undesirable adverse reactions from these combined studies is presented below.

Headache was the most frequently reported and only very commonly reported adverse reaction (30%).

Other adverse reactions reported in the clinical trials with a frequency below 10% are listed in the table.

| Organ system | Common adverse event (>1/100, <1/10): | Uncommon adverse events (>1/1000, <1/100): | Rare adverse events (>1/10000, <1/1000): |
|--------------------------------|--|---|---|
| <i>Cardiovascular</i> | Edema | Slight rise of blood pressure, hypertension | Myocardial infarction, deep venous thrombosis, pulmonary embolism and other embolisms |
| <i>Neoplasms</i> | | | Cervical cancer, breast cancer |
| <i>Genital tract</i> | Intermenstrual bleeding, spotting, amenorrhea, vaginal candidiasis | | |
| <i>Breast</i> | Tenderness | Galactorrhea, pain, enlargement | |
| <i>Gastro-intestinal tract</i> | Abdominal cramps, bloating | Nausea, vomiting, colitis | |
| <i>Skin</i> | Acne, rash | Alopecia, hirsutism, chloasma | Erythema (nodosum, multiforme) |
| <i>Central nervous</i> | Migraine, mood | Irritability, changes | |

| <i>system</i> | changes, depression | in libido | |
|------------------|--|---------------------|--|
| <i>Metabolic</i> | Fluid retention, changes in body weight (increase or decrease) | Changes in appetite | |

Listed below are adverse reactions that have been associated with the use of hormonal contraceptives:

Cardiovascular system: cerebrovascular accidents, arterial thromboembolism, myocardial infarction, hypertension.

Neoplasms: benign liver tumors, malignant hepatic tumors.

Hepatobiliary: intrahepatic cholestasis, cholelithiasis, cholestatic jaundice, Budd-Chiari syndrome.

Genital tract: absence of withdrawal bleeding, change in menstrual flow, increase in size of uterine fibromyoma, increase in cervical erosion and secretion, temporary infertility after discontinuation of treatment, premenstrual syndrome.

Breast: diminution in lactation when given immediately post-partum.

Skin and subcutaneous tissue: seborrhea, hypertrichosis, pemphigoid (herpes gestationis), melasma which may persist, hemorrhagic eruption, urticaria and angioedema.

Eyes: change in corneal curvature (steepening), intolerance to contact lenses, xerophthalmia.

Central nervous system: chorea, severe headache.

Metabolic: reduced glucose tolerance.

4.9 Overdose

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives. Overdosage may cause nausea, vomiting and, in young girls, vaginal bleeding. There are no antidotes and treatment should be symptomatic.