

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Logynon Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each light brown tablet contains:

Ethinylestradiol	30 micrograms
Levonorgestrel	50 micrograms

Each white tablet contains:

Ethinylestradiol	40 micrograms
Levonorgestrel	75 micrograms

Each ochre-coloured tablet contains:

Ethinylestradiol	30 micrograms
Levonorgestrel	125 micrograms

Excipients: Each tablet also contains lactose and sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet.

Product imported from the UK:

Each calendar-blister contains 6 light brown sugar-coated tablets, 5 white sugar-coated tablets and 10 ochre-coloured sugar-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oral contraception

4.2 Posology and method of administration

Method of administration

Oral use

Dosage regimen

How to take Logynon

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.

The memo-pack contains 21 tablets. Tablet-taking is always started from the section marked “Start” and then continued daily in the direction of the arrows.

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, during which time a withdrawal bleed usually occurs.

This usually starts on day 2-3 after the last coated tablet and may not have finished before the next pack is started.

How to start Logynon

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). Starting on days 2-5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

Changing from a combined hormonal contraceptive (combined oral contraceptive /COC), vaginal ring, or transdermal patch)

The woman should start with Logynon preferably on the day after the last hormone-containing tablet of her previous COC, but at the latest on the day following the usual tablet-free or hormone-free tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Logynon 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 any day from the minipill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due), but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

Following first-trimester abortion

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second-trimester abortion

For breastfeeding women see Section 4.6

Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, 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.

Management of missed tablets

If the user is **less than 12 hours** late in taking any 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 she is **more than 12 hours** late in taking any tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. tablet-taking must never be discontinued for longer than 7 days
2. 7 days of uninterrupted 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*

The user should take the last missed tablet as soon as she remembers, even if this means taking two 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. The more tablets are missed and the closer they are to the regular tablet-free interval, the higher the risk of a pregnancy.

- *Week 2*

The user should take the last missed tablet as soon as she remembers, even if this means taking two 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 tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

- *Week 3*

The risk of reduced reliability is imminent because of the forthcoming tablet-free interval. 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 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 user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next pack must be started as soon as the current pack is finished, i.e., no gap should be left between packs. The user is unlikely to have a withdrawal bleed until the end 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 first normal tablet-free interval, the possibility of pregnancy should be considered.

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 or severe diarrhoea occurs within 3-4 hours after tablet-taking, the advice concerning missed tablets, as given in 'Management of missed tablets', 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.

In case of persisting or recurrent gastrointestinal disturbances, additional contraceptive measures should be taken and the physician should be informed.

How to shift periods or how to delay a period

To delay a period the woman should continue with the last 10 tablets of another pack of Logynon without a tablet-free interval. The extension can be carried on for a maximum of 10 days, until the end of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of Logynon is then resumed after the usual 7-day tablet-free 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 tablet-free 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).

Additional information on special populations

Children and adolescents

Logynon is only indicated after menarche.

Geriatric patients

Not applicable. Logynon is not indicated after menopause.

Patients with hepatic impairment

Logynon is contraindicated in women with severe hepatic diseases. See also section 'Contraindications'.

Patients with renal impairment

Logynon 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 Precautions for Use").
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- 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 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 listed in section 6.1.

4.4 Special warnings and 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 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, stroke, deep venous thrombosis and pulmonary embolism and of cerebrovascular accidents. These events occur rarely.

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 (COC) 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 initially starts using a COC or when she restarts COC use after a pill-free interval of at least a month. 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, 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 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.

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.

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 (for information on "Pregnancy and Lactation" see Section 4.6).

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic 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

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).

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 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.

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; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss, depression.

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 and/or cholestasis related pruritus 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 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 while taking COCs.

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

Each coated tablet of 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.

Each coated tablet contains sucrose: Patients with rare hereditary problems of fructose intolerance, glucosegalactose, malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Medical examination/consultation

Prior to the initiation or reinstitution of COC use, a complete medical history and physical examination should be taken guided by the contraindications (Section 4.3) and warnings (section 'Warnings') and should be repeated periodically and pregnancy must be ruled out. 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.

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 e.g. missed tablets (section 'Management of missed tablets'), vomiting or diarrhoea (section 'Advice in case of gastro-intestinal disturbances') during tablet taking or concomitant medication (Section 4.5).

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

Effects of other medicaments on Logynon

Interactions of other drugs (enzyme inducers, some antibiotics) with oral contraceptives may impair the contraceptive efficacy and/or 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 liver 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 during the use of the antibiotics and 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.

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

- ***Enzyme induction (increase of hepatic metabolism):*** Interactions can occur with drugs that induce hepatic 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).

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

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, 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Logynon is not indicated during pregnancy. If pregnancy occurs during treatment with Logynon, 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. These amounts may affect the child.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of COCs.

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*:

System Organ Class	Common (≥ 1/100)	Uncommon (≥ 1/1000 and < 1/100)	Rare (< 1/1000)
Eye disorders			Contact lens intolerance
Gastrointestinal disorders	Nausea, Abdominal pain	Vomiting, Diarrhoea	
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 pain, Breast tenderness	Breast hypertrophy	Vaginal discharge, Breast discharge
Skin and subcutaneous tissue disorders		Rash, Urticaria	Erythema nodosum, Erythema multiforme

* The most appropriate MedDRA term (version 12.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed but should be taken into account as well.

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
- 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

Pharmacotherapeutic group (ATC): Progestogens and estrogens, fixed combinations ATC Code: G03AA

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.

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

As well as protection against pregnancy, COCs have several positive properties which, next to the negative properties (see Warnings, Undesirable effects), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. Apart from this, there is evidence of a reduced risk of endometrial cancer and ovarian cancer. Furthermore, the higher dosed COCs (0.05 mg ethinylestradiol) have been shown to reduce the incidence of ovarian cysts, pelvic inflammatory disease, benign breast disease and ectopic pregnancy. Whether this also applies to lower-dosed COCs remains to be confirmed.

5.2 Pharmacokinetic properties

○ Levonorgestrel

Absorption

Orally administered levonorgestrel is rapidly and completely absorbed. Maximum levonorgestrel concentrations in serum of 2.3 ng/ml are reached about 1 hour after start of treatment with Logynon. Following single ingestion of 0.125 mg levonorgestrel together with 0.03 mg ethinylestradiol (which represents the combination with the highest levonorgestrel content of the triphasic formulation), peak serum concentrations of 4.3 ng/ml are reached at about 1 hour after single ingestion. Levonorgestrel is almost completely bioavailable after oral administration.

Distribution

Levonorgestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1.4 % of the total serum drug concentrations are present as free steroid, 55% are specifically bound to SHBG and about 44% are non-specifically bound to albumin. The ethinylestradiol-induced increase in SHBG influences the proportion of levonorgestrel 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 levonorgestrel is about 128 l after single oral administration of the highest levonorgestrel dose of Logynon.

Metabolism

Levonorgestrel is completely metabolized by the known pathways of steroid metabolism. The clearance rate from serum is approximately 1.0 ml/min/kg after single oral administration of the highest levonorgestrel dose of Logynon.

Elimination

Levonorgestrel serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of approximately 22 hour. Levonorgestrel is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1:1. The half-life of metabolite excretion is about 1 day.

Steady-state conditions

Levonorgestrel pharmacokinetics are influenced by SHBG levels, which are increased about twofold during the 21 days treatment period with Logynon. Following daily ingestion drug serum levels increase about fourfold reaching steady-state conditions during the second half of a treatment cycle. At steady-state, the volume of distribution and the clearance rate are reduced to 52 l and 0.5 ml/min/kg, respectively.

○ Ethinylestradiol

Absorption

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 116 pg/ml are reached within 1.3 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 sulphate. The clearance rate was reported to be 2.3 - 7 ml/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. At the end of treatment, the maximum ethinylestradiol concentration of about 132 pg/ml is reached after about 1.3 h.

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 tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose
maize starch
povidone
talc
sucrose
magnesium stearate (E572)
polyethylene glycol 6000
calcium carbonate (E170)
glycerin (E422)
titanium dioxide (E171)
ferric oxide pigment yellow (E172)
ferric oxide pigment red (E172)
montan glycol wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer packaging of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Each calendar blister strip contains 6 light brown sugar-coated tablets, 5 white sugar-coated tablets and 10 ochre-coloured sugar-coated tablets.

Presentation
Cartons containing 1 x 21 tablets.

6.6 Special precautions for disposal and other handling

No special requirement

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Clear Pharma Limited
157-173 Roden Street
Belfast BT12 5QA
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1823/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th March 2014

10 DATE OF REVISION OF THE TEXT