SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TriRegol coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

6 pink tablets: each tablet contains 30 micrograms ethinylestradiol and 50 micrograms levonorgestrel 5 white tablets: each tablet contains 40 micrograms ethinylestradiol and 75 micrograms levonorgestrel
10 ochre tablets: each tablet contains 30 micrograms ethinylestradiol and 125 micrograms levonorgestrel

Excipients with known effect: each tablet contains 31.35 mg of lactose (as lactose monohydrate, which is 33 mg) and 22 mg of sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet.

Pink, bright, biconvex, circular tablets

White, bright, biconvex, circular tablets

Ochre, bright, biconvex, circular tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception

4.2 Posology and method of administration

Posology.

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 bleeding will usually begin on the 2nd or 3rd day after ingestion of the last tablet and it may not have ceased, before the next pack is started.

How to start the use of Triregol

No preceding intake of hormonal contraceptives (within the last month)
Tablet-taking started on day 1 of the woman's natural cycle (=the first day of her menstrual bleeding). Starting intake on day 2-5 is allowed, but during the first cycle the concurrent use of barrier method during the first 7 days of tablet intake is advisable.

Changing from another combined hormonal contraceptive (combined oral contraceptive, contraceptive vaginal ring, contraceptive transdermal patch)
The woman should start with Triregol on the day after she took the last active tablet in her previous blister pack of contraceptive pills (or removed the transdermal patch or vaginal ring), or no later than on the day after the usual pill-free (or placebo, patch-free or ring-free) interval with her previous contraceptive.

Changing from a progestogen-only method (progestogen-only pills, injectable, implant)
The woman can change from progestogen-only pills on any day (changing from implant on the day of its removal; changing from injection when the next injection should have been given). In all these cases concurrent use of a barrier method during the first 7 days of tablet intake is advisable.

After abortion in 1st trimester
The woman may begin intake of tablets immediately. If she so does, it is not necessary to take further contraceptive measures.

After delivery or abortion in 2nd trimester
For breast-feeding women - see section 4.6.
The woman should be advised to start on day 21-28 after delivery or abortion in 2nd trimester, since there is an increased risk of thromboembolism during the post-partum period. She should be advised to use a barrier method concurrently during the first 7 days of tablet intake if she starts later. If she has already had intercourse, pregnancy must be excluded before she starts tablet intake, or she must await her first menstrual bleeding.

Missed tablets

If a tablet is delayed by less than 12 hours, additional contraception is unnecessary and the remaining tablets are taken as usual.
If the delay exceeds 12 hours, contraceptive protection may be reduced. Handling of missed tablets may be managed by the following two basic rules:

- Tablets must never be discontinued for longer than 7 days.
- Seven days of uninterrupted tablet taking are required to maintain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Thus, the following advice may be given for daily practice:

Week 1
The user must take the last missed tablet as soon as she remembers, even if this means that she has to take 2 tablets at the same time. Thereafter, she should continue taking the tablets at the usual time of the day. She must also use a barrier method of contraception, e.g. a condom, for the next 7 days. If intercourse has taken place during the preceding 7 days the possibility of pregnancy must be considered. The more missed tablets and the closer to the tablet-free interval this happens, the greater the risk of pregnancy.

Week 2
The user must take the last missed tablet as soon as she remembers even if this means that she has to take 2 tablets at the same time. Thereafter, she continues taking the tablets at the usual time of the day. Provided that the tablets have been taken in a correct manner during the 7 days preceding the missed tablet, it is not necessary to take further contraceptive measures. However, if this is not the case, or if more than 1 tablet has been missed, the woman should be advised to use an other contraceptive method for 7 days.

Week 3
The risk of contraceptive failure is imminent because of the ensuing tablet-free interval. Thus, it is not necessary to take further contraceptive measures if one of the two alternatives below is followed, provided that all tablets have been taken in a correct manner during the 7 days preceding the missed tablet. If this is not the case, the woman should be advised to follow the first of the two alternatives and concurrently use an other contraceptive method for the next 7 days.

The user should take the last missed tablet as soon as she remembers, even if it means that she has to take 2 tablets at the same time. Thereafter she should continue taking the tablets at the usual time of the day. She should then start the next pack immediately after taking the last tablet in the current pack , i.e. without a tablet-free interval between the packs. Withdrawal bleeding is unlikely until the end of the second pack, but there may be some spotting, or break-through bleeding, on the days she is taking tablets.
The woman may also be advised to stop taking tablets from the current pack. In that case, she should keep a period without tablets of up to 7 days, including those days when she forgot to take her tablets, and thereafter continue with the next pack.

If a woman has missed tablets and then does not get a withdrawal bleed in the first normal tablet-free interval, the possibility of pregnancy must be considered.

Advice in case of gastro-intestinal disturbances

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

If vomiting or severe diarrhoea occurs within 3 to 4 hours after taking a tablet, the woman should apply the advice concerning missed tablets.

How to delay or shift a period
The woman should continue with the last 10 ochre tablets of the second pack Triregol without keeping the period without tablets, in order to delay the menstrual bleeding. If the woman wishes to delay for more than 10 days, she should use a pack of a monophasic COC with similar or higher progestogen dose. After the desired delay has been reached, regular intake of Triregol can be resumed after a pill-free period of 7 days.

To shift her period to another day of the week, women may be advised to shorten the forthcoming tablet-free interval by as many days as she likes. The shorter the interval, the higher the risk that she will not have a withdrawal bleed and may experience breakthrough bleeding or spotting during the second pack. It is important to emphasise that the pill free interval should not be extended.

Paediatric population
There is no relevant use of TriRegol coated tablets in the paediatric population before the pubertal age.

Method of administration

For oral use.

The tablets must be taken orally in the order directed on the blister package at about the same time every day, with some liquid if necessary.

4.3 Contraindications

Combined oral contraceptives (COCs) are not to be used in the presence of any of the following 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) with or without provoking factor (see section 4.4).
- 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 tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Pregnancy or suspected pregnancy (see section 4.6).
- Severe hypertension.
- Ocular disorder of vascular origin.
– Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Triregol is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.4 and 4.5).

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 and discussed with the woman before she decides to 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 whether COC use should be discontinued.

Circulatory disorders
Epidemiological studies have shown that the incidence of venous thromboembolism (VTE) in users of oral contraceptives with low oestrogen content (<50 microgram 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 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 microgram ethinylestradiol is approximately 20 cases per 100,000 women-years of use. Epidemiological studies have also associated the use of 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 hormonal contraceptive 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).

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

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

When weighing benefits/disadvantages the physician must take into consideration that adequate treatment of a given condition may lower the risk related to thrombosis and that the risk of developing thrombosis during pregnancy is higher compared to using contraceptive pills.

Tumours
An increased risk of cervical cancer in long-term users of COC 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 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 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.

Other conditions

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.
Women who get severely depressed during the use of contraceptive pills should stop taking the pills and be advised to use an alternative contraceptive method while trying to determine if the symptoms are due to the oral contraceptive preparation. Women who have previously suffered from depression should be closely monitored and stop the use of the oral contraceptive preparation if the symptoms of depression relapse.

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

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired 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. Steroid hormones may be poorly metabolised in patients with impaired liver function.

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.

Hyperlipidaemic women should be closely monitored if they choose to use COCs.

<u>Medical examination/consultation</u>

Prior to the initiation or reinstitution of ethinylestradiol/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 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 effect of COCs may be reduced, in the event of missed tablets, vomiting, diarrhoea or concomitant mediciation.

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.

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

ALT elevations
During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). ALT elevations have also been observed with HCV anti-viral medicinal products containing glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.3 and 4.5).

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. Patients who are on a lactose free diet should take this amount into consideration.

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction

Pharmacodynamic interactions

Concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir, with or without ribavirin, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir may increase the risk of ALT elevations (see sections 4.3 and 4.4). Therefore, Triregol users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these drug regimens. Triregol can be restarted 2 weeks following completion of treatment with these drug regimens.

Pharmacokinetic interactions

Effects of other medicinal products on TriRegol coated tablets
Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

Management
Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Short-term treatment
Women on treatment with enzyme inducing drugs should temporarily use a barrier method or another method of contraception in addition to the COC. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation.
If the drug therapy runs beyond the end of the tablets in the COC pack, the next COC pack should be started right after the previous one without the usual tablet-free interval.

Long-term treatment
In women on long-term treatment with enzyme-inducing active substances, another reliable, nonhormonal, method of contraception is recommended.

The following interactions have been reported in the literature.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction) e. g.:
Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (*Hypericum perforatum*).

Substances with variable effects on the clearance of COCs
When co-administered with COCs, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of estrogen or progestins. The net effect of these

changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Effects of TriRegol coated tablets on other medicinal products
Oral contraceptives may affect the metabolism of certain other active substances. Accordingly, plasma and tissue concentrations may be affected:

Clinical data suggests that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

Ciclosporin
Oral contraceptives may inhibit the hepatic metabolism of ciclosporin resulting in increased adverse events.

Lamotrigine
COCs have been shown to induce metabolism of lamotrigine resulting in sub-therapeutic plasma concentrations of lamotrigine.

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

Laboratory tests

The use of contraceptive steroids may have an influence on the results of certain laboratory analyses, including biochemical parameters for liver, thyroid, adrenal and kidney function; the plasma levels of (transport)-proteins, e.g. corticosteroid-binding globulin and lipid/lipoprotein fractions; parameters for carbohydrate metabolism and parameters for coagulation and fibrinolysis. Changes usually remain within the normal laboratory reference values.

Note

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Triregol is contraindicated in confirmed or suspected pregnancy (see section 4.3). If pregnancy occurs during medication with Triregol, treatment should be withdrawn immediately.

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.

Breast-feeding
Lactation may be influenced by contraceptive pills as they may reduce the amount of the 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 of the breast milk. Small amounts of contraceptive steroids and/or their metabolites may be excreted in milk. These amounts may affect the child.

4.7 Effects on ability to drive and use machines

Triregol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most frequently adverse reactions do usually not demand interruption of treatment and include: depression, mood altered headache nausea, vomiting, abdominal pain, cholelithiasis, acne, chloasma, breast tenderness, breast pain, metrorrhagia and weight increased.

For serious adverse experiences in users of oral contraceptives see section 4.4.

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

System Organ Class	*Common* ≥1/100 to ≤1/10	*Uncommon* ≥1/1,000 to ≤1/100	*Rare* ≥1/10,000 to ≤1/1,000	*Very rare* ≤1/10,000	*Not known (cannot be estimated from the available data)*
Immune system disorders			Hypersensi-tivity		Exacerbation of symptoms of hereditary and acquired angioedema
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		Breast cancer		Hepatic adenoma, Hepatic neoplasm malignant	
Metabolism and nutrition disorders		Fluid retention	Hyperlipi-daemia		Hypercholes-terolaemia, Hypertrigly-ceridaemia

Psychiatric disorders	Depression, Mood changes	Libido decreased, Libido increased, Loss of libido, Nervousness			Irritability
Nervous system disorders	Headache	Migraine		Cerebrovas-cular accident, Sydenham's chorea	Cerebrovas-cular disorder, Epilepsy aggravated, Dizziness
Eye disorders			Contact lens intolerance	Visual disturbance	
Ear and labyrinth disorders			Otosclerosis		
Cardiac disorders				Myocardial infarction	
Vascular disorders		Hyperten-sion	Venous thrombo-embolism		Arterial thrombo-embolism, Pulmonary embolism, Phlebitis
Gastrointestina l disorders	Nausea Abdominal pain	Diarrhoea, Vomiting	Colitis ulcerative, Crohn's disease	Pancreatitis	
Hepatobiliary disorders	Cholelithiasis				Jaundice cholestatic
Skin and subcutaneous tissue disorders	Acne, Chloasma	Rash, Urticaria	Erythema multiforme, Erythema nodosum		Hypertricho-sis, Seborrhoea
Musculoskelet al and connective tissue disorders				Systemic lupus erythema-tosus	Sensation of heaviness
Reproductive system and breast disorders	Breast tenderness, Breast pain, Metrorrhagia	Breast enlargement	Breast discharge, Vaginal discharge		Amenorrhoea, Anovulatory cycle, , Oligomeno-rrhoea
Investigations	Weight increased		Weight decreased		

Interactions
Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with oral contraceptives (see section 4.5).

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 COC 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There have been no reports of serious, harmful effects after overdose. The symptoms which may occur in connection with overdose are: Nausea, vomiting and, in young girls, slight vaginal bleeding. There is no antidote, and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormonal contraceptives for systemic use; Progestogens and estrogens, sequential preparations, ATC CODE: G03AB03

The contraceptive action of oral contraceptives is based on interaction of different factors, of which the most important is the inhibition of ovulation and changes in cervical mucus and the endometrium. In addition to protection against pregnancy contraceptive pills have several positive effects. The cycle becomes more regular, the menstrual bleeding is often less painful, and the bleeding is less heavy. The latter may result in a decrease in the occurrence of iron deficiency. In addition it has been demonstrated that high-dose oral contraceptives (50 µg ethinylestradiol) reduces the risk of fibrocystic tumours in the breast, ovarian cysts, pelvic infection, ectopic pregnancy and endometrial and ovarian cancer. Whether this also applies for low-dose oral contraceptives remains to be confirmed.

5.2 Pharmacokinetic properties

Levonorgestrel

Absorption

After oral administration of Triregol, levonorgestrel is rapidly and completely absorbed (bioavailability approximately 100%) and it does not undergo a first-pass metabolism.

Distribution
Levonorgestrel is to a large extent bound to albumin and SHBG (Sex Hormon Binding Globulin) in plasma.

Biotransformation
The most important metabolism occurs at reduction of the Δ4-3-oxo group and hydroxylation at the positions 2α, 1β and 16β, followed by conjugation. Most of the metabolites circulating in the blood are sulphates of 3α, 5β-tetrahydro-levonorgestrel, while the excretion mainly takes place as glucuronides. Some of the original levonorgestrel is also circulating as 17β-sulphate. There is a large interindividual variation in values of metabolism clearance and this may partly explain the large variations observed in levonorgestrel concentrations among users.

Elimination
Levonorgestrel is eliminated with a mean half-life of approximately 36 hours at steady state. Levonorgestrel and its metabolites are primarily excreted in the urine (40% to 68%) and approximately 16% to 48% is excreted in faeces.

Ethinylestradiol

Absorption
Ethinylestradiol is rapidly and completely absorbed. Peak plasma levels are reached after 1.5 hours. As a consequence of presystemic conjugation and first-pass metabolism the absolute bioavailability is 60%. The area under the curve and C_{max} may be expected to rise slightly over time.

Distribution
Ethinylestradiol is 98.8% bound to plasma proteins, almost exclusively to albumin.

Biotransformation
Ethinylestradiol undergoes presystemic conjugation both in the mucosa of the small intestine and in the liver. Hydrolysis of the direct conjugates of ethinylestradiol with the aid of the intestinal flora gives ethinylestradiol, which can be re-absorbed, and an enterohepatic circulation is hereby set up. The primary pathway of ethinylestradiol metabolism is cytochrome P-450-mediated hydroxylation in which the primary metabolites are 2-OH-ethinylestradiol and 2-methoxy-ethinylestradiol. 2-OH-ethinylestradiol is further metabolised to chemically reactive metabolites.

Elimination
Ethinylestradiol disappears from plasma with a half-life of approximately 29 hours (26-33 hours), plasma clearance varies from 10-30 L/hour. The conjugates of ethinylestradiol and its metabolites are excreted via urine and faeces (ratio 1:1).

5.3 Preclinical safety data

Acute toxicity of ethinylestradiol and levonorgestrel is low. Because of marked species differences preclinical results possess a limited predictive value for the application of estrogens in humans.
In experimental animals estrogens displayed an embryolethal effect at relatively low doses; malformations of the urogenital tract and feminisation of male fotuses were observed.

Levonorgestrel displayed a virilising effect in female fotuses. Reproduction toxicology studies in rats, mice and rabbits revealed no indication of teratogenicity.
Preclinical data based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential revealed no particular human risks beyond those discussed in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pink tablets:
Core: colloidal anhydrous silica; magnesium stearate; talc; maize starch; lactose monohydrate;

Coating: colloidal anhydrous silica; talc; carmellose sodium; povidone K30; macrogol 6000; copovidone K28; calcium carbonate; sucrose; red iron oxide (E172); titanium dioxide (E171).

White tablets:
Core: colloidal anhydrous silica; magnesium stearate; talc; maize starch; lactose monohydrate;

Coating: colloidal anhydrous silica; talc; carmellose sodium; povidone K30; macrogol 6000; copovidone K28; calcium carbonate; sucrose; titanium dioxide (E171).

Ochre tablets:
Core: colloidal anhydrous silica; magnesium stearate; talc; maize starch; lactose monohydrate;

Coating: colloidal anhydrous silica; talc; carmellose sodium; povidone K30; macrogol 6000; copovidone K28; calcium carbonate; sucrose; yellow iron oxide (E172); titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

Aluminium-PVC/PVDC blister

Pack sizes: 1 x 21 tablets, 3 x 21 tablets, 6 x 21 tablets and 13 x 21 tablets.
Not all pack sizes may be marketed.

Each blister contains 21 tablets (6 pink tablets, 5 white tablets and 10 ochre tablets).

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

8 MARKETING AUTHORISATION NUMBER(S)

PL 04854/0123

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/06/2007

10 DATE OF REVISION OF THE TEXT

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