Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trinordiol Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each light brown tablet contains 50 micrograms levonorgestrel and 30 micrograms ethinylestradiol.

Each white tablet contains 75 micrograms levonorgestrel and 40 micrograms ethinylestradiol.

Each ochre tablet contains 125 micrograms levonorgestrel and 30 micrograms ethinylestradiol.

Excipients with known effect:
Each tablet contains 33mg lactose monohydrate and 19mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet.

Each blister pack contains 6 light brown, 5 white, and 10 ochre, lustrous sugar coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormonal contraception.

4.2 Posology and method of administration

Posology

Paediatric population
No data are available.

Safety and efficacy of combined oral contraceptive (COCs) have been established in adult women of reproductive age.

Elderly
COCs are not indicated for use in postmenopausal women.

Method of administration

How to take Trinordial
Regular daily intake of tablets for 21 consecutive days is important for the preservation of contraceptive efficacy.

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 tablet and may not have finished before the next pack is started.

How to start Trinordial

No hormonal contraceptive use in the preceding month

The user should begin taking Trinordiol on Day 1 of her natural menstrual cycle (i.e. the first day of her menstrual bleeding). Beginning Trinordiol use on days 2-7 of the menstrual is allowed, however a nonhormonal back-up method of birth control (such as, condoms and spermicide) is recommended during for the first 7 days of Trinordiol use.

Switching from another combined oral contraceptive (COC)

Preferably, Trinordiol use should begin on the day after the last active tablet of her previous COC pack has been taken, but no later than the day following the usual tablet-free or inactive tablet interval of the previous COC.

Switching from a progestin only method of birth control (pill, implant, intrauterine device [IUD], injection)

The user may discontinue use of a progestin only pill on any day; use of Trinordiol should begin the following day. Trinordiol use begin on the same day that a progestin only implant or a progestin only IUD is removed. In each of these situations, the user should be advised to use a nonhormonal back-up method of birth control during the first 7 days of Trinordiol use.

Following first trimester abortion

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

Postpartum

Because the immediate post-partum period is associated with an increased risk of thromboembolism, Trinordiol use should begin no sooner than the day 28th postpartum day after delivery or second-trimester abortion. The woman should be advised to additionally use a back-up method for the first 7 days of tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of Trinordiol use or the woman has to wait for her first menstrual period before beginning Trinordiol use. See sections 4.4 and 4.6.

Management of missed tablets

Contraceptive protection may be reduced if tablets are missed particularly if the missing of tablets extends the tablet-free interval. If tablets were missed in the first week of the cycle and intercourse took place in the week before the tablets were missed, the possibility of a pregnancy should be considered.

Provided that the user is **less than 12 hours late** in taking any tablet, she should take it as soon as she remembers and further tablets should be taken at the usual time.

If she is **more than 12 hours late** in taking any tablet, contraceptive protection may be reduced.

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets in one day. She then continues to take tablets at her usual time. In addition, a back-up method such as the condom should be used for the next 7 days.

If these 7 days run beyond the last tablet in the current pack, the next pack must be started as soon as the current pack is finished; no gap should be left between packs. This prevents an extended break in tablet taking thereby reducing the risk of escape ovulation. 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.

If the user does not have a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be ruled out before resuming tablet taking from the next pack.

In case of gastrointestinal upset

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 a period
To delay a period the woman should continue taking the tablets from the last active phase (ochre tablets) from another pack of Trinordiol without a tablet-free interval. The extension can be carried on for as long as wished until the all the tablets are completed. During the extension the woman may experience breakthrough-bleeding or spotting.

Regular intake of Trinordiol is then resumed after the usual 7 day tablet-free interval.

4.3 Contraindications

Oral contraceptives should not be used in women with any of the following conditions. Should any of the conditions appear for the first time during COC use, the product must be stopped immediately:

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Venous thrombosis present or in history (deep vein thrombosis, pulmonary embolism)
- Arterial thrombosis present or in history (e.g. myocardial infarction)
- Thrombophlebitis or thromboembolic (arterial or venous) disorders or other diseases, associated with an increased thromboembolic risk such as thrombogenic valvulopathies and thrombogenic rhythm disorders (current or history)
- 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 section 4.4)
- Hereditary or acquired predisposition for venous or arterial thrombosis (see section 4.4)
- Cerebrovascular accident or coronary artery disease present or in history
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal vaginal bleeding
- Hepatic adenomas or carcinomas, or severe liver disease, current or previous, as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant)
- Pancreatitis associated with severe hypertriglyceridemia (current or history)
- Uncontrolled hypertension
- Diabetes mellitus with vascular involvement
- History of migraine with focal neurological symptoms, such as aura
- Known or suspected pregnancy

Trinordiol is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

4.4 Special warnings and precautions for use

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

For any particular estrogen/progestin combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestin that is compatible with a low failure rate and the needs of the individual patient.

The use of COCs is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and hypertension. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidaemia, obesity, and particularly diabetes with vascular involvement.

Circulatory Disorders
1. Thromboembolic Disorders and Other Vascular Problems

Oral contraception must be used with caution in women with risk factors for thrombotic and thromboembolic events or cardiovascular disease. Any of the following risk factors for venous or arterial disease may constitute an unacceptable level of risk.

a. Myocardial Infarction
An increased risk of myocardial infarction has been attributed to oral-contraceptive use.

Smoking in combination with oral-contraceptive use has been shown to contribute substantially to the incidence of myocardial infarction in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non smokers over the age of 40 among women who use oral contraceptives.

All women who use oral contraceptives should be strongly advised not to smoke.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors. The risk of arterial thromboembolic complications in COC users increases with:

- increasing age
- smoking (women over 35 years should be strongly advised not to smoke if they wish to use a COC)
- dyslipoproteinemia
- hypercholesterolemia
- hypertension
- valvular heart disease
- migraine
- atrial fibrillation
- obesity (body mass index over 30 kg/m^2)
- diabetes

b. Venous Thrombosis and Thromboembolism

Epidemiological studies have shown that the incidence of venous thromboembolism (VTE) in users of oral contraceptives with low estrogen content (<50 mcg 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 COC 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 cases.

The overall absolute risk (incidence) of VTE for levonorgestrel containing combined oral contraceptives with 30 micrograms ethinylestradiol is approximately 20 cases per 100,000 woman 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.

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.

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

- increasing age
- A positive family history (venous thromboembolism ever in a sibling or parent at 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 immobilization, 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 resume

until two weeks after complete remobilization. Antithrombotic treatment should be considered if the pills have not been discontinued in advance.
- obesity (body mass index over 30 kg/m^2)
- recent delivery or second trimester abortion (see section 4.2)

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 a COC)
- dyslipoproteinemia
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation
- obesity (body mass index over 30 kg/m^2)

The presence of one serious or multiple risk factors for venous or arterial disease, respectively, can also constitute a contra-indication.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The Health Care Practitioner should warn the patient to contact their physician immediately if they experience possible symptoms of thrombosis and discontinue the COC promptly.

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 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, hemolytic uremic syndrome and 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).

c. Cerebrovascular Disease

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension has been found to be a risk factor for both users and nonusers, for both types of strokes, while smoking appears to increase the risk for hemorrhagic stroke. Transient ischaemic attacks have also been associated with oral contraceptive use.

COC users with migraine (particularly migraine with aura) may be at increased risk of stroke.

2. Carcinoma of the Reproductive Organs

Tumors

a. Cervical cancer

The most important risk factor for cervical cancer is persistent human papilloma virus infection.

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).

b. Breast cancer

A meta-analysis from 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 increased risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the lifetime risk of breast cancer. 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. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

3. Hepatic Neoplasia/Liver Disease

In rare cases, benign liver tumors, and even more rarely, malignant liver tumors have been reported in users of COCs. In isolated cases, these tumors have lead to life-threatening intra abdominal haemorrhages. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.

Studies have shown an increased risk of developing hepatocellular carcinoma and hepatic adenoma in long-term oral contraceptive users; however, these cancers are extremely rare.

Women with a history of COC-related cholestasis and women who develop cholestasis during pregnancy are more likely to develop cholestasis with COC use. Such patients who use COCs should be carefully monitored, and COC use should be discontinued if cholestasis recurs.

Hepatocellular injury has been reported with COC use. Early identification of drug-related

hepatocellular injury can decrease the severity of hepatotoxicity when the drug is discontinued. If hepatocellular injury is diagnosed, patients should stop their COC, use a non-hormonal form of contraception and consult their doctor.

Acute or chronic disturbances of liver function may necessitate the discontinuation of the COC use until liver function has returned to normal.

4. Other Conditions

a. Ocular Lesions

There have been case reports of retinal thrombosis with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

b. Gallbladder Disease

An increased relative risk of gallbladder disease in users of oral contraceptives and estrogens has been reported in some studies.

c. Carbohydrate and Lipid Metabolic Effects
Glucose intolerance has been reported in oral contraceptive users. Some progestins are known to increase insulin secretion and create insulin resistance, while estrogens (> 75 mg) may create a state of hyperinsulinism. Women with impaired glucose tolerance or diabetes mellitus should be carefully observed while taking oral contraceptives, particularly in the early stage of COC use. However there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

Some progestins may elevate low-density lipoproteins (LDL) levels and may render the control of hyperlipidemias more difficult. Non hormonal contraception should be considered in women with uncontrolled dyslipidemias.

d. Hypertension
Although small increases in blood pressure have been reported in many women taking COC's, clinically relevant increases are rare and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomised trials have shown that the incidence of hypertension increases with increasing quantities of progestins.

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.

Women with a history of hypertension or hypertension-related diseases, or renal diseases should be encouraged to use another method of contraception.

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

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

f. Angioedema
Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

g. Liver function
Acute or chronic liver dysfunction may necessitate the discontinuation of COC use until liver function returns to normal. Steroid hormones may be poorly metabolised in patients with impaired liver function. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

h. Emotional disorders
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.

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

i. Folate levels
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.

j. St. John's wort
If combined oral contraceptives (COCs) and St. John's wort are used concomitantly, a non-hormonal back-up method of birth control is recommended (see section 4.5).

k. Other
Diarrhoea and/or vomiting may reduce hormone absorption resulting in decreased serum concentration (see section 4.5).

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.

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, gallstones, porphyria, systemic lupus erythematosus, haemolytic uremic syndrome, Sydenham´s chorea, herpes gestationis, otosclerosis-related hearing loss.

Physical Examination and Follow-up
Prior to the initiation or reinstitution of Trinordiol 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 (see section 4.3) and warnings (see 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 examinations should be based on established practice guidelines and be adapted to the individual woman and if judged appropriate by the clinician, should include breast, abdominal and pelvic examination including cervical cytology.

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

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

Reduced cycle control
With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. The type and dose of progestin may be important. 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.

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

Patients with rare hereditary problems of fructose intolerance, galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Trinordiol.

4.5 Interaction with other medicinal products and other forms of interaction

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

During concomitant use of COC- products and substances that may lead to decreased COC serum concentrations, it is recommended that a nonhormonal back-up method of birth control (such as condoms and spermicide) be used in addition to

the regular intake of Trinordiol. In the case of prolonged use of such substances COCs should not be considered the primary contraceptive.

With liver enzyme inducing drugs, a non-hormonal back-up method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation.

Examples of substances that may decrease serum COC concentrations:

- Any substance that reduces gastrointestinal transit time and, therefore, COC absorption.
- Substances that induce hepatic microsomal enzymes, such as carbamazepine, oxycarbamazepine, rifampicin, rifabutin, barbiturates, primidone, phenylbutazone, griseofulvin, topiramate modafinil, dexamethasone, some protease inhibitors, phenytoin, and possibly also felbamate. 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.
- St. John's wort: Breakthrough bleeding and unintended pregnancies have been reported in women taking COCs and St. John's wort (*Hypericum perforatum*). St. John's wort may induce microsomal enzymes, which theoretically may result in reduced clinical efficacy of COCs. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's wort. If COCs and St. John's wort are used concomitantly, a non-hormonal backup method of birth control is recommended.

After discontinuation of substances that may lead to decreased COC serum concentrations, use of a non-hormonal back-up method is recommended for at least 7 days. Longer use of a back-up method is advisable after discontinuation of substances that have lead to induction of hepatic microsomal enzymes, resulting in decreased COC serum concentrations. If the drug therapy runs beyond the end of the tablets in the COC pack, the next COC pack should be started without the usual tablet-free interval.

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.

Examples of substances that may increase serum COC concentrations:

- atorvastatin
- competitive inhibitors for sulfation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and paracetamol
- substances that inhibit cytochrome P450 3A4 isoenzymes, such as indinavir, fluconazole and troleandomycin

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

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

In patients treated with flunarizine, use of oral contraceptives has been reported to increase the risk of galactorrhea.

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

In women on chronic treatment with hepatic enzyme inducing medications, COCs are not recommended unless other more appropriate methods are not available or acceptable.

Pharmacodynamic interactions

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

Therefore, Trinordiol users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with these combination drug regimens. Trinordiol can be restarted 2 weeks following completion of treatment with these combination drug regimens.

4.6 Fertility, pregnancy and lactation

Pregnancy

Ethinylestradiol/levonorgestrel is not indicated during pregnancy.

If pregnancy occurs during treatment with COCs, further intake must be stopped. However, extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect at unintentional intake of contraceptive pills in early pregnancy.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

For serious adverse effects when taking COCs, see section 4.4. For thromboembolic events, lipid disorders, gallbladder diseases, breast cancer, see also section 4.4.

The most frequently (greater than 10%) reported adverse events during phase III studies and post marketing surveillance in women using Trinordiol are headache, including migraines and breakthrough bleeding/spotting.

Use of COCs has been associated with an increased risk of the following:

- venous thromboembolic disorders
- arterial thromboembolic disorders
- cervical intraepithelial neoplasia and cervical cancer
- being diagnosed with breast cancer
- liver tumors (e.g. focal nodular hyperplasia, hepatic adenoma)
- hypertension
- Crohn's disease, ulcerative colitis, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, hemolytic 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 and 4.4.

Other adverse events have been reported in women taking Trinordial:

System organ class	**Frequency of adverse events**				
	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not Known (cannot be estimated from the available data)
Infections and infestations		Vaginitis, including candidiasis			
Immune system disorders				Hypersensitivity, anaphylactic/anaphylactoid reactions including very rare cases of urticaria, angioedema and severe reactions with respiratory and circulatory symptoms	Exacerbation of symptoms of hereditary and acquired angioedema
Metabolism and nutrition disorders			Changes in appetite (increase or decrease), fluid retention	Glucose intolerance	
Psychiatric disorders		Mood changes, including depression, libido decreased, libido increased			
Nervous system disorders	Headache, migraine	Nervousness, dizziness			
Eye disorders				Intolerance to contact lenses	
Gastrointestinal disorders		Nausea, abdominal pain, vomiting	Abdominal cramps, bloating, diarrhoea,		
Hepatobiliary disorder				Cholestatic jaundice	
Skin and subcutaneous tissue disorders		Acne	Rash, chloasma (melasma) which may persist, hirsutism, alopecia, urticaria	Erythema nodosum, erythema multiforme	
Reproductive system breast disorders	Breakthrough bleeding and spotting	Breast pain, tenderness, breast enlargement, dysmenorrhea, change in menstrual flow, change in cervical ectropion and secretion, amenorrhea		Breast discharge, vaginal discharge	
General disorders and administration site conditions		Fluid retention/oedema			

Investigations		Weight increase, weight decreased	Increase in blood pressure, changes in serum lipid levels, including hypertriglyceridemia	Decrease in serum folate levels (serum folate levels may be depressed by COC therapy)	

The following adverse events have been classified as very rare adverse events (<1/10,000):

- exacerbation of systemic lupus erythematosus
- exacerbation of porphyria
- exacerbation of chorea
- optic neuritis (optic neuritis may lead to partial or complete loss of vision)
- aggravation of varicose veins
- retinal vascular thrombosis
- pancreatitis
- ischaemic colitis
- hepatic adenomas
- hepatocellular carcinomas
- gallbladder disease, including gallstones (COCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.)
- haemolytic uremic syndrome

The frequency of the following adverse effect is unknown: hepatocellular injury (e.g. hepatitis, hepatic function abnormal), inflammatory bowel disease (Crohn's disease, ulcerative colitis).

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 HPRA Pharmacovigilance. Website: www.hpra.ie

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, sequential preparations
ATC code: G03AB03

Ethinylestradiol is a synthetic estrogen which has actions and uses similar to those of estradiol, but is more potent.

Norgestrel is a progestational agent with actions similar to those of progesterone. It is much more potent as an inhibitor of ovulation than norethisterone and has androgenic activity.

Trinordiol is a combination oral contraceptive (COC) containing ethinyl estradiol (EE) and levonorgestrel. COCs have been shown to exert their effect by decreasing gonadotropin secretion to suppress ovarian activity. The resulting contraceptive effect is based on various mechanisms, the most important of which is the inhibition of ovulation.

5.2 Pharmacokinetic properties

Absorption
Ethinylestradiol is absorbed by the gastro-intestinal tract.

Biotransformation
It is only slowly metabolised and excreted in the urine. Norgestrel is absorbed from the gastro-intestinal tract.

Elimination
Metabolites are excreted in the urine and faeces as glucuronide and sulfate conjugates.

5.3 Preclinical safety data

No pre-clinical safety data other than those described elsewhere in this document are considered relevant to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Maize starch
Talc
Magnesium stearate
Povidone K25

Coating:
Sucrose
Macrogol 6000
Calcium carbonate
Titanium dioxide
Povidone K90
Glycerol
Wax E Pharma (Montanglycol Wax E)
Iron oxide pigment, red brown E172 (light brown tablets)
Iron oxide pigment, yellow E172 (light brown and ochre tablets)
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Primary container: Polyvinylchloride (PVC)/aluminium foil blister pack.

Secondary container: Cardboard carton.
Each blister strip may also be packaged in an aluminium foil pouch together with a silica gel desiccant sachet which should be discarded on opening.

Presentation: Memo pack containing 21 tablets (6 light brown tablets (50 micrograms levonorgestrel/30 micrograms ethinylestradiol), 5 white tablets (75 micrograms levonorgestrel/40 micrograms ethinylestradiol), 10 ochre tablets (125 micrograms levonorgestrel/30 micrograms ethinylestradiol)).

Cardboard carton contains 3 blister packs.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland Unlimited Company
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8 MARKETING AUTHORISATION NUMBER

PA0822/100/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 February 1981

Date of last renewal: 02 February 2006

10 DATE OF REVISION OF THE TEXT

December 2024