# הודעה על החמרה ( מידע בטיחות) בעלון לרופא

**תאריך 07.05.2012**

**שם תכשיר באנגלית**  Harmonet

**מספר רישום**  121-88-30272-00

**שם בעל הרישום** Neopharm Ltd. Hashiloach 6, POB 7063, Petach Tiqva 49170

החמרות בעלון מסומנות על רקע צהוב

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| **פרטים על השינוי/ים המבוקש/ים** | | |
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **4.2 Posology and method of administration** | In Case Of Gastrointestinal Upset | PAEDIATRIC POPULATION  Paediatric data are not available. Safety and efficacy of COCs have been established in adult women of reproductive age.  GERIATRIC POPULATION  COCs are not indicated for use in postmenopausal women.  In Case Of Gastrointestinal Upset  If vomiting or diarrhoea occurs within 4 hours after the tablet taking, tablet absorption may be incomplete. Use of tablets from a backup pack is required, as outlined in the section Management of missed tablets (4.2 above). |
| **4.3 Contraindications** |  |  Pancreatitis associated with severe hypertriglyceridaemia (current or history) |
| **4.4 Special warnings and precautions for use** |  | WARNINGS  **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.**  COC users with migraine (particularly migraine with aura)may be at increased risk of stroke.  See section 4.3  Venous Thrombosis and Thromboembolism  Epidemiological studies have shown that the incidence of VTE in women with no known risk factors for VTE who use low dose oestrogen (<50 mcg ethinylestradiol) combined oral contraceptives ranges from about 20 cases per 100,000 woman-years (for levonorgestrel- containing COCs) to 40 cases per 100,000 women-years (for desogestrel/gestodene- containing COCs).  Use of COCs increases the risk of venous thrombotic and thromboembolic events. |
|  | 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  relatively early age)   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/m2)  The presence of one serious or multiple risk factors, depending on type and severity, for venous or arterial disease, may constitute an unacceptable level of risk  There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.  2. Carcinoma of the Reproductive OrgansSome studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors  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.  Women with a history of COC-related cholestasis or women with cholestasis during pregnancy are more likely to have this condition with COC use. If these patients receive a COC they should be carefully monitored and, if the condition recurs, the COC should be discontinued  7. Hypertension  An increase in blood pressure has been reported in women taking oral contraceptives 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 randomized trials have shown that the incidence of hypertension increases with increasing quantities of progestins.  Women with a history of hypertension or hypertension-related diseases, or renal diseases should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued.  8. Headache  9. Bleeding Irregularities  Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. The type and dose of progestin may be important. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, continued use of the oral contraceptive or a change to another formulation may solve the problem.  In some women, withdrawal bleeding may not occur during the usual tablet free interval. If the COC has been taken according to directions, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to directions prior to the first missed withdrawal bleed or if two consecutive withdrawal bleeds are missed, pregnancy should be ruled out  PRECAUTIONS FOR USE  1. Physical Examination and Follow-up  A complete personal and family medical history and physical examination should be taken prior to the initiation of COC use, and should be repeated periodically during the use of COCs. The physical examination should include special reference to blood pressure, breasts, abdomen, and pelvic organs,including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.  Patients should be counselled that this product does not protect against HIV infection (AIDS)  and other sexually transmitted diseases.  2. Lipid Disorders | 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  relatively early age)   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/m2)   Recent delivery or second trimester abortion (see section 4.2)  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.  Carcinoma of the Reproductive  Organs  *a. Cervical cancer*  The most important risk factor for cervical cancer is persistent human papillomavirus infection.  Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behaviour and other factors. See section 4.4 (*9. Bleeding Irregularities.)*  *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 very rare cases, benign hepatic adenomas and in extremely rare cases, hepatocellular carcinoma may be associated with COC use. The risk appears to increase with duration of COC use. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.  ……  Women with a history of COC-related cholestasis or 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 birth control 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  7. Hypertension  An increase in blood pressure has been reported in women taking oral contraceptives 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 randomized trials have shown that the incidence of hypertension increases with increasing quantities of progestins.  Women with a history of hypertension or hypertension-related diseases, or renal diseases should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued.  COC use is contraindicated in women with uncontrolled hypertension (see 4.3).  8. *Migraine/*Headache  9. Bleeding Irregularities  Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. The type and dose of progestin may be important. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, continued use of the oral contraceptive or a change to another formulation may solve the problem.  In some women, withdrawal bleeding may not occur during the usual tablet free interval. If the COC has been taken according to directions, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to directions prior to the first missed withdrawal bleed or if two consecutive withdrawal bleeds are missed, tablet-taking should be discontinued and a nonhormonal back-up method of contraception should be used until the possibility of pregnancy is be ruled out.  Some women may encounter post-pill amenorrhea (possibly with anovulation) or oligomenorrhea, especially when such a condition was preexistent.  10. Angioedema  Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema.  PRECAUTIONS FOR USE  1. Physical Examination and Follow-up  Prior to the initiation or reinstitution of Harmonet 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.  2. Lipid Disorders  *Glucose intolerance has been reported in COC users. Woman with impaired glucose tolerance or diabetes mellitus who use COCs should be carefully monitored. See section 4.5* |
| **4.5 Interaction with other medicinal products and other forms of interaction** | Examples of substances that may decrease serum EE concentrations:  RitonavirAny substance that reduces gastrointestinal transit time and, therefore, EE absorption  Substances that induce hepatic microsomal enzymes, such as carbamazepine, oxycarbamazepine, rifampicin, rifabutin, barbiturates, primidone, phenylbutazone,  phenytoin, griseofulvin, topiramate, and modafinil, Certain antibiotics (eg, ampicillin and other penicillins, tetracyclines), by a decrease of enterohepatic circulation of estrogens  After discontinuation of substances that may lead to decreased EE 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 EE serum concentrations. It may sometimes take several weeks until enzyme induction has completely subsided, depending on dosage, duration of use and rate of elimination of the inducing substance  Examples of substances that may increase serum EE 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.  EE 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 (eg, ciclosporin and theophylline, 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. | Examples of substances that may decrease serum EE concentrations:  Any substance that reduces gastrointestinal transit time and, therefore, EE absorption  Substances that induce hepatic microsomal enzymes, such as carbamazepine, oxycarbamazepine, rifampicin, rifabutin, barbiturates, primidone, phenylbutazone,  phenytoin, griseofulvin, topiramate, modafinil, dexamethasone, some protease inhibitors  Certain antibiotics (eg, ampicillin and other penicillins, tetracyclines), by a decrease of enterohepatic circulation of estrogens  After discontinuation of substances that may lead to decreased EE 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 EE serum concentrations. Maximal enzyme induction is generally not seen for 2-3 weeks but may then be sustained for at least 4 weeks after cessation of drug therapy.  Examples of substances that may increase serum EE 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.  EE 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 (eg, cyclosporine, 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. |
| **4.6 Pregnancy and lactation** | HARMONET is not indicated during pregnancy.  Before commencing a treatment with HARMONET pregnancy has to be excluded. If pregnancy occurs during use with HARMONET treatment should be withdrawn immediately.  Extensive epidemiological studies have revealed no increased risk of birth defects in children born to women who used COCs prior to pregnancy. Most epidemiological studies also do not suggest a teratogenic effect; particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when combinations of estrogens and progestogens in dose levels relevant for HARMONET or other COCs were taken inadvertently during early pregnancy. Studies in animals have shown reproductive toxicity, including adverse effect on the development of the female urogenital system.  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 contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. | If pregnancy occurs during treatment with COCs, further intake should be discontinued. There is no conclusive evidence that the estrogen and progestin contained in the COC will damage the developing child if conception accidentally occurs during COC use, See section 4.3  LACTATION  Small amounts of contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement.  The use of COCs is generally not recommended until the nursing mother has completely weaned her child. |
| **4.8 Undesirable effects** | For serious adverse effects in COC users see 4.4 “Special warnings and precautions for use”**.** For thromboembolic events, lipid disorders, gallbladder diseases, breast cancer, see also section 4.4. “Special warnings and precautions for use”. The most frequently (greater than  10%) reported adverse events during phase III studies and postmarketing surveillance in women using HARMONET are headache, including migraines and breakthrough bleeding/spotting. | For serious adverse effects in COC users see 4.4 “Special warnings and precautions for use”**.** For thromboembolic events, lipid disorders, gallbladder diseases, breast cancer, see also section 4.4. “Special warnings and precautions for use”. The most frequently (greater than  10%) reported adverse events during phase III studies and postmarketing surveillance in women using HARMONET are headache, including migraines and breakthrough bleeding/spotting.  Use of COCs has been associated with an increased risk of the following:   Arterial and venous thrombotic and thromboembolic events   Cervical intraepithelial neoplasia and cervical cancer   Being diagnosed with Breast cancer   Benign hepatic tumors (eg. focal nodular hyperplasia, hepatic adenoma)   |  |  | | --- | --- | |  | **Very**  **Common**   **10%** | | Infections and  Infestations |  | | Immune system  disorders |  | | Metabolism and  nutrition disorders |  | | Psychiatric  disorders |  | | Nervous system  disorders | Headache,  including migrane | | Eye disorders |  | | Gastrointestinal  disorders |  | | Hepato-biliary  disorder |  | | Skin and  subcutaneous tissue disorders |  | | Reproductive  system and  breast disorders | Breakthrough  bleeding and  spotting | | General  disorders and  administration |  | | Investigations |  |   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). |
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