

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Harmonet 75 microgram/20 microgram coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 75 micrograms gestodene and 20 micrograms ethinylestradiol.

Excipients with known effect:

Each tablet contains 37.505mg lactose and 19.661mg sucrose

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Coated tablet.

White, sugar coated tablet with a shiny surface.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oral hormonal contraception

The decision to prescribe Harmonet should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Harmonet compares with other CHCs (see sections 4.3 and 4.4).

4.2 Posology and method of administration

PAEDIATRIC POPULATION

Paediatric data are not available. Safety and efficacy of CHCs have been established in adult women of reproductive age.

GERIATRIC POPULATION

CHCs are not indicated for use in postmenopausal women.

HOW TO TAKE HARMONET

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 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 HARMONET

No hormonal contraceptive use within the preceding month

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

Switching from another combined hormonal contraceptive (CHC)

Preferably Harmonet use should begin on the day after the last active tablet of the previous CHC, but no later than the day following the usual tablet-free or inactive tablet interval of the previous CHC.

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

The user may discontinue use of the progestin only pill on any day; use of Harmonet should begin the following day. Harmonet use should begin on the same day that a progestin only implant or a progestin only IUD is removed. Harmonet use should begin on the day that the next progestin only injection is scheduled.

In each of these situations, the user should be advised to additionally use a back-up method of birth control during for the first 7 days of Harmonet 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, Harmonet use should begin no sooner than the 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 Harmonet use or the woman has to wait for her first menstrual period before beginning Harmonet use. (See section 4.4: Thromboembolism and section 4.6)

MANAGEMENT OF MISSED TABLETS

Contraceptive protection may be reduced if tablets are missed and 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

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)

HOW TO DELAY A PERIOD

To delay a period the woman should continue with another pack of Harmonet without a tablet-free interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting.

Regular intake of Harmonet 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:

- Presence or risk of venous thromboembolism (VTE)
 - Thrombophlebitis or venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE]) or other diseases, associated with an increased thromboembolic risk such as thrombogenic valvulopathies and thrombogenic rhythm disorders (current or history)
 - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
 - Major surgery with prolonged immobilization (see section 4.4)
 - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)
- Presence or risk of arterial thromboembolism (ATE)
 - Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
 - Cerebrovascular or coronary artery disease – current stroke, history of prodromal condition (e.g. transient ischaemic attack, TIA)
 - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant)
 - History of migraine with focal neurological symptoms
 - A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
 - Diabetes mellitus with vascular symptoms
 - Severe hypertension
 - Severe dyslipoproteinaemia
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal vaginal bleeding
- Hepatic adenomas or carcinomas, or acute or chronic liver disease, as long as liver function has not returned to normal
- Pancreatitis associated with severe hypertriglyceridaemia (current or history)
- Known or suspected pregnancy
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Warnings

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.

If any of the conditions or risk factors mentioned below is present, the suitability of Harmonet should be discussed with the woman.

In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of Harmonet should be discontinued.

Risk of Venous Thromboembolism

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as Harmonet may have up to twice this level of risk. The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with Harmonet, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.**

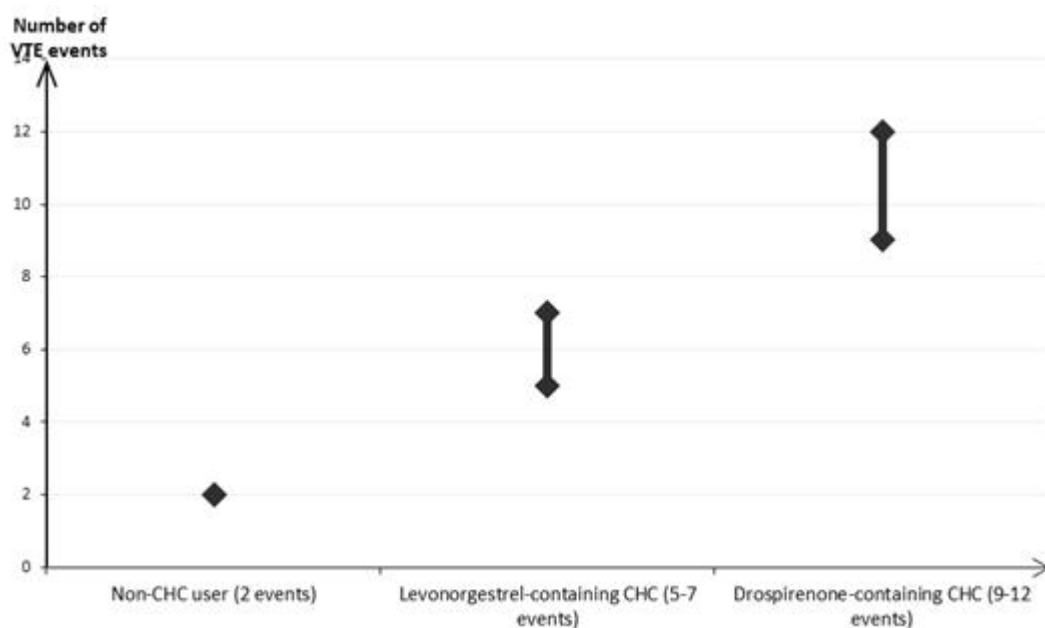
In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

It is estimated¹ that out of 10,000 women who use a CHC containing [progestogen] between 9 and 12 women will develop a VTE in one year; this compares with about 6² in women who use a levonorgestrel-containing CHC.

In both cases, the number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period.

VTE may be fatal in 1-2% of cases.

Number of VTE events per 10,000 women in one year



¹ These incidences were estimated from the totality of the epidemiological study data, using relative risks for the different products compared with levonorgestrel-containing CHCs.

² Mid-point of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6

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 hormonal contraceptives ranges from about 20 cases per 100,000 woman-years (for levonorgestrel-containing CHCs) to 40 cases per 100,000 women-years (for desogestrel/gestodene-containing CHCs).

For CHCs containing 30µg of ethinylestradiol combined with desogestrel or gestodene compared with those containing less than 50µg of ethinylestradiol and levonorgestrel, the overall risk of venous thrombotic and thromboembolic events has been estimated to range between 1.5 and 2.0. The incidence of venous thrombotic or thromboembolic events for levonorgestrel containing CHCs with less than 50µg of ethinylestradiol is approximately 20 cases per 100,000 woman-years of use. For CHCs containing 30µg of ethinylestradiol combined with desogestrel or gestodene the incidence is approximately 30-40 cases per 100,000 woman-years of use, i.e. additional 10-20 cases per 100,000 woman-years of use.

Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

Risk factors for VTE

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table).

Harmonet is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	Comment
Obesity (body mass index over 30 kg/m ²)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation (including air travel >4 hours), major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors	In these situations it is advisable to discontinue use of the patch/pill/ring (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Harmonet has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease
Increasing age	Particularly above 35 years

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

The increased risk of thromboembolism in pregnancy, and particularly the 6 week period of the puerperium, must be considered (for information on "Pregnancy and lactation" see section 4.6; see also graph on VTE risk).

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or

- walking,
 - increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:

- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden coughing which may be associated with haemoptysis;
- sharp chest pain;
- severe light headedness or dizziness;
- rapid or irregular heartbeat.

Some of these symptoms (e.g. “shortness of breath”, “coughing”) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE

The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). Harmonet is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for ATE

Risk factor	Comment
Increasing age	Particularly above 35 years
Smoking	Women should be advised not to smoke if they wish to use a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	
Obesity (body mass index over 30 kg/m ²)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors
Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Migraine	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation
Other medical conditions associated	Diabetes mellitus, hyperhomocysteinaemia,

with adverse vascular events	valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.
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Symptoms of ATE

In the event of symptoms, women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of a cerebrovascular accident can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- sudden trouble walking, dizziness, loss of balance or coordination;
- sudden confusion, trouble speaking or understanding;
- sudden trouble seeing in one or both eyes;
- sudden, severe or prolonged headache with no known cause;
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of MI can include:

- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone;
- discomfort radiating to the back, jaw, throat, arm, stomach;
- feeling of being full, having indigestion or choking;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeats.

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 (*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 CHCs. The increased risk gradually disappears during the course of the 10 years after cessation of CHC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent CHC 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 CHC users, the biological effects of CHCs or a combination of both. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Hepatic Neoplasia/Liver Disease

In very rare cases, benign hepatic adenomas and in extremely rare cases, hepatocellular carcinoma may be associated with CHC use. The risk appears to increase with duration of CHC use. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

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

Women with a history of CHC-related cholestasis or women who develop cholestasis during pregnancy are more likely

to develop cholestasis with CHC use. Such patients who use CHCs should be carefully monitored and, CHC use should be discontinued if cholestasis recurs.

Hepatocellular injury has been reported with CHC 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 CHC, 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 CHC use until liver function has returned to normal.

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.

Gallbladder Disease

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

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 (> 75µg) may create a state of hyperinsulinism. Women with impaired glucose tolerance or diabetes mellitus should be carefully observed while taking oral contraceptives. Due to alterations of glucose tolerance, the required dose of insulin or other antidiabetic agents might change. A small proportion of women will have persistent hypertriglyceridaemia while on the pill. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents.

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.

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

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.

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 CHC has been taken according to directions, it is unlikely that the woman is pregnant. However, if the CHC 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 ruled out.

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

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema.

Precautions

Medical examination/ consultation

Prior to the initiation or reinstatement 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 contraindications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of Harmonet compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

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.

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

Lipid Disorders

Glucose intolerance has been reported in CHC users. Women with impaired glucose tolerance or diabetes mellitus who use CHCs should be carefully monitored. See section 4.5

A small proportion of women will have adverse lipid changes while taking oral contraceptives. Persistent hypertriglyceridemia may occur in a small proportion of CHC users. Elevations of plasma triglycerides may lead to pancreatitis and other complications. Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestins may elevate low-density lipoprotein (LDL) levels and may render the control of hyperlipidemias more difficult. Non-hormonal contraception should be considered in women with uncontrolled dyslipidemias (see Warnings).

Liver function

Acute or chronic liver dysfunction may necessitate the discontinuation of CHC use until liver function returns to normal. Steroid hormones may be poorly metabolized in patients with impaired liver function.

Emotional disorders

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.

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.

St. John's wort

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

Other

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

The following conditions have been reported to occur or deteriorate with both pregnancy and CHC use, but the evidence of an association with CHC use is inconclusive: jaundice and/or pruritus related to cholestasis, porphyria, systemic lupus erythematosus, haemolytic uremic syndrome, Sydenham's chorea, herpes gestationis, otosclerosis-related hearing loss.

This medicinal product contains lactose and sucrose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Harmonet.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between ethinylestradiol (EE) and other substances may lead to decreased or increased serum EE concentrations.

Decreased EE serum concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the CHC.

During concomitant use of EE-containing products and substances that may lead to decreased EE serum concentrations, it is recommended that a non-hormonal back-up method of birth control (such as condoms and spermicide) be used in addition to the regular intake of HARMONET. In the case of prolonged use of such substances CHCs should not be considered the primary contraceptive.

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 (e.g. ampicillin and other penicillins, tetracyclines), by a decrease of enterohepatic circulation of estrogens
- St. John's wort: Breakthrough bleeding and unintended pregnancies have been reported in women taking CHCs and St. John's wort (*Hypericum perforatum*). St. John's wort may induce microsomal enzymes, which theoretically may result in reduced clinical efficacy of CHCs. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's wort. If CHCs 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 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 led 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 co-administration with CHCs.

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

(e.g. 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, CHCs are not recommended unless other more appropriate methods are not available or acceptable.

4.6 Fertility, pregnancy and lactation

Pregnancy

If pregnancy occurs during treatment with CHCs, further intake should be discontinued. There is no conclusive evidence that the estrogen and progestin contained in the CHC will damage the developing child if conception accidentally occurs during CHC use, see section 4.3.

The increased risk of VTE during the postpartum period should be considered when re-starting Harmonet (see sections 4.2 and 4.4).

Breast-feeding

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 CHCs is generally not recommended until the nursing mother has completely weaned her child.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Description of selected adverse reactions

An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

For serious adverse effects in CHC users see section 4.4. For 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 Harmonet are headache, including migraines and breakthrough bleeding/spotting.

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

- Cervical intraepithelial neoplasia and cervical cancer
- Being diagnosed with Breast cancer
- Benign hepatic tumours (e.g. focal nodular hyperplasia, hepatic adenoma)

Other adverse events have been reported in women taking CHC:

	Very Common ≥ 10%	Common ≥1% and <10%	Uncommon ≥ 0.1% and < 1%	Rare ≥0.01% and <0.1%
Infections and Infestations		Vaginitis, including candidiasis		
Immune system disorders				Anaphylactic/anaphylactoid reactions, including very rare cases of urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms.
Metabolism and nutrition disorders			Changes in appetite (increase or decrease)	Glucose intolerance
Psychiatric disorders		Mood changes, including depression, changes in libido		
Nervous system disorders	Headache, including migraine	Nervousness, dizziness		Stroke, transient ischaemic attack
Eye disorders				Intolerance to contact lenses
Cardiac Disorders				Myocardial infarction
Vascular disorders				Arterial thromboembolism, venous thromboembolism
Respiratory, thoracic and mediastinal disorders				Pulmonary embolism
Gastrointestinal disorders		Nausea, vomiting, abdominal pain	Abdominal cramps, bloating	
Hepato-biliary disorder				Cholestatic jaundice
Skin and subcutaneous tissue disorders		Acne	Rash, chloasma (melasma), which may persist, hirsutism, alopecia	Erythema nodosum
Reproductive system and breast disorders	Breakthrough bleeding and spotting	Breast pain, tenderness, enlargement, secretion, dysmenorrhoea, change in menstrual flow, change in cervical ectropion and secretion, amenorrhoea		
General disorders and administration		Fluid retention/oedema		
Investigations		Changes in weight (increase or decrease)	Increase in blood pressure, changes in serum lipid levels, including	Decrease in serum folate levels (Serum folate levels may be depressed by CHC)

			hypertriglyceridemia	levels)
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The following adverse events have been classified as very rare adverse events (<0.01%):

- 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 (CHCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.)
- Erythema multiforme
- 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 HPRC Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: <http://www.hpra.ie/>; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of oral contraceptive overdosage in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote, and further treatment of overdose, if necessary, is directed to the symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations
ATC Code: G03AA10

Single-phase oestrogen-progestogen combination. Non-corrected Pearl index: 0.24 (21,521 cycles).

The contraceptive efficacy of Harmonet arises from three complementary mechanisms of action:

- Ovulation is inhibited at the level of the hypothalamo-hypophysial axis,
- Cervical secretions become impermeable to the migration of spermatozooids,
- The endometrium becomes unsuitable to nidation.

5.2 Pharmacokinetic properties

Ethinylestradiol:

Absorption

Ethinylestradiol is rapidly and completely absorbed after oral ingestion. After administration of 15 µg, peak plasma

concentrations of 30 pg/mL are reached after 1- 1.5 hours. Ethinylestradiol undergoes an extensive first pass effect, which displays great inter-individual variation. The absolute bioavailability is approximately 45%.

Distribution

Ethinylestradiol has an apparent volume of distribution of 15 L/kg and binding to plasma proteins is approximately 98%. Ethinylestradiol induces the hepatic synthesis of sex-hormone binding globulins (SHBG) and corticoid-binding globulins (CBG). During treatment with 15µg ethinylestradiol the plasma concentration of SHBG increases from 86 to about 200 nmol/L.

Metabolism

Ethinylestradiol is metabolised completely (metabolic plasma clearance approximately 10mL/min/kg). The metabolites formed are excreted in the urine (40%) and faeces (60%).

Elimination

The elimination half-life of ethinylestradiol is approximately 15 hours. Ethinylestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinylestradiol are excreted at a urinary to biliary ratio of 4 : 6.

Steady state conditions

Steady state conditions are reached during the second half of the treatment cycle and serum levels of ethinylestradiol accumulate by a factor of about 1.4 to 2.1.

Gestodene:

Absorption

After oral administration gestodene is rapidly and completely absorbed. The absolute bioavailability is about 100%. After oral intake of a single 60 µg gestodene dose, peak plasma concentrations of 2ng/mL are reached in about 60 minutes. The plasma concentrations are strongly dependent on the SHBG concentrations.

Distribution

Gestodene has an apparent volume of distribution of 1.4 L/kg following a single 60 µg dose. It is 30% bound to plasma albumin and 50-70% bound to SHBG.

Metabolism

Gestodene is extensively metabolised by the steroid metabolic pathway. The metabolic clearance is about 0.8mL/min/kg following a single 60 µg dose. The non-active metabolites formed are excreted in urine (60%) and faeces (40%).

Elimination

The apparent elimination half-life of gestodene is about 13 hours. The half-life is prolonged to 20 hours after concomitant administration with ethinylestradiol.

Steady state conditions

After multiple dosing concomitantly with ethinylestradiol the plasma concentration increases approximately by a factor of 2-4.

5.3 Preclinical safety data

Toxicological studies have been performed on all components individually and on their combination. Acute toxicity studies in animals showed no evidence of a risk of acute symptoms arising after accidental overdosage.

General safety studies with repeated administration have shown no evidence of any effects suggesting any unexpected risks in man.

Long term and repeated dose carcinogenicity studies have not demonstrated any carcinogenic potential; however, it is important to remember that sex steroids are capable of promoting the development of certain tissues into hormone-dependent tumours.

Teratogenicity studies have not indicated any particular risk when oestrogen-progestogen combinations are used correctly; it is however essential to discontinue treatment immediately if taken in error at the beginning of pregnancy.

Mutagenicity studies have not revealed any mutagenic potential for ethinylestradiol or gestodene.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose,
Maize starch,
Povidone,
Magnesium stearate,
Sucrose,
Macrogol,
Calcium carbonate,
Talc,
Wax E.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep blister in the outer carton to protect from light.

6.5 Nature and contents of container

Primary Container:
PVC/Aluminium foil blister pack .

Secondary Container: Cardboard carton.

The blister strip may be packaged in an aluminium foil pouch together with a silica gel desiccant sachet which should be discarded on opening.

Presentation: Pack containing 1 blister of 21 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0822/066/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 September 2003

Date of last renewal: 05 September 2008

10 DATE OF REVISION OF THE TEXT

October 2014