# Harmonet* Tablets
# (75 micrograms Gestodene / 20 micrograms Ethinyloestradiol)

## 1. NAME OF THE MEDICINAL PRODUCT

HARMONET Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 75 micrograms gestodene and 20 micrograms ethinyloestradiol.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Coated tablets

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Hormonal contraception.

The decision to prescribe Harmonet should take into consideration the user's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Harmonet compares with that of other combined hormonal contraceptives (CHC) (see sections 4.3 and 4.4).

### 4.2 Posology and method of administration

Do not start or continue using Harmonet if you are pregnant or suspect you are pregnant.

How to take Harmonet

Tablets must be taken in the order directed on the package, every day at about the same time, with a small amount of liquid. 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. Bleeding usually starts 2-3 days after the last tablet and may still continue when the next pack is started.

How to start using Harmonet

*No preceding hormonal contraceptive use [in the past month]*
Tablet-taking should start on the first day of the natural cycle (i.e. on the first day of menstrual bleeding). Starting on days 2-7 is also possible; in this case, it is recommended that during the first cycle, another method of birth control [condoms, spermicide] is also used during the first seven days of tablet-taking.

*Switching from another combined oral contraceptive (COC)*
Preferably Harmonet use should begin on the day after the last active tablet of the previous COC, but at the latest, on the day following the usual tablet-free or inactive tablet interval of the previous COC.

*Switching from a progestin only product (minipill, injection, implant, intrauterine device (IUD))*
The woman may switch from the progestin-only pill to Harmonet on any day, beginning the use of Harmonet the following day. After removal of an implant or an IUD, use of Harmonet should begin on the day of removal. If using an injection, the Harmonet tablet should be taken on the same day when the next injection would be due. In all of these situations, a method of birth control should also be used for the first seven days of tablet-taking.

*Following first-trimester abortion*
Use of the tablets may be started immediately. In this case, additional contraceptive measures are not needed.

*Postpartum*
Because the immediate post-partum period is associated with an increased risk of thromboembolism, COCs should be started no earlier than day 28 after delivery (if the mother does not breast-feed) or second-trimester abortion. The woman should be advised to additionally use a method of birth control for the first 7 days of tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period (see section 4.6).

Missing a tablet

Contraceptive reliability may be reduced if tablets are missed and particularly if the tablet-free interval is extended.

- If a tablet is missed and is **less than 12 hours** late, the user should take it as soon as she remembers and subsequent tablets should be taken at the usual time.
- If a tablet is missed and is **more than 12 hours** late, contraceptive protection may be reduced.
    - The woman should take the last missed tablet as soon as she remembers it, even if this means taking two tablets in one day. The next tablets should be taken at the usual time. In addition, an additional method of birth control (such as condoms) should be used for the next 7 days.
    - If the 7-day period during which an additional method of birth control is used runs beyond the current pack, the next pack must be started as soon as the current pack is finished; i.e. no tablet-free interval should be left between packs. This prevents an extended break in tablet-taking which may increase the risk of escape ovulation. A withdrawal bleed is not likely to occur until the end of the second pack, but spotting or breakthrough bleeding may occur on tablet-taking days.
    - If a withdrawal bleed has not occurred at the end of the second pack, the possibility of pregnancy must be ruled out before resuming tablet-taking.

Instructions related to vomiting and/or diarrhoea

If vomiting or diarrhoea occurs within 4 hours after tablet-taking, absorption of the product may be incomplete. In such an event, the instructions **Missing a tablet** are applicable. The woman must take the necessary extra tablets from another pack.

Delaying the menstrual bleeding

To delay the menstrual bleeding, the woman may continue with another pack of Harmonet immediately after finishing the previous pack, without the tablet-free interval. The extension can be carried on for as long as wished, however at most 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.

Paediatric population

The safety and efficacy of COCs have been evaluated in women of reproductive age. These products are not indicated for children or adolescents before the first menstrual period has started.

Elderly

COCs are not indicated for use in postmenopausal women.

**4.3 Contraindications**

Combined hormonal contraceptives (CHCs) should not be used in women with any of the following conditions:

- Presence or risk of venous thromboembolism (VTE)
  - Venous thromboembolism - current VTE (patients on anticoagulants) or history of VTE (e.g., deep venous thrombosis [DVT] or pulmonary embolism)
  - 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 immobilisation (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
  - Arterial thromboembolism – presence or history of arterial thromboembolism (e.g., myocardial infarction) or prodromal condition (e.g., *angina pectoris*)
  - Cerebrovascular disease – presence or history of stroke or 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
- Thrombophlebitis or a history of deep vein thrombophlebitis
- Thrombogenic valvulopathies
- Thrombogenic rhythm disorders
- Known or suspected breast cancer
- Endometrial cancer or other known or suspected oestrogen-dependent neoplasia
- Undiagnosed vaginal bleeding
- Cholestatic jaundice associated with pregnancy or jaundice prior to COC use
- Hepatic adenoma or carcinoma, or active liver disease, as long as liver function values have not returned to normal
- Known or suspected pregnancy
- Pancreatitis or a history of pancreatitis if associated with confirmed severe hypertriglyceridaemia
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Concomitant use of medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir/glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir with Harmonet tablets is contraindicated (see section 4.5).

**4.4 Special warnings and precautions for use**

**Warnings**

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 user should be advised to contact a doctor to determine whether the use of Harmonet should be discontinued.

**The risk of serious cardiovascular adverse reactions related to COC use increases with age and heavy smoking (at least 15 cigarettes per day) and is relatively marked in women over 35 years of age. Therefore, women who use COCs should be strongly advised to stop smoking.**

***1. Venous and Arterial Thrombosis and Thromboembolism***

Risk of Venous Thromboembolism (VTE)

The use of any CHC increases the risk of venous thromboembolism (VTE) compared with no use. Products containing 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 of a CHC. There is

also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks.

For any particular oestrogen/progestin combination, the dosage regimen prescribed should be one which contains the least amount of oestrogen and progestin, has been found to be reliable, and meets the patient's needs.

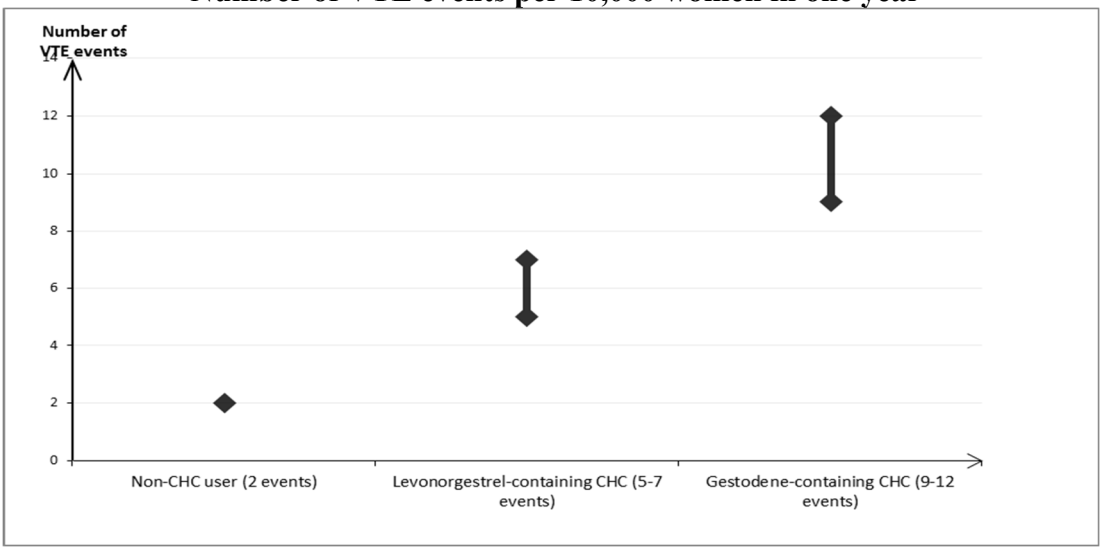
If the patient has not taken COCs previously, she should first be prescribed a product which contains less than 50 µg of oestrogen.

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

It is estimated that out of 10,000 women who use a gestodene-containing CHC, about 9-12[1] will develop VTE in one year. In women who use a levonorgestrel-containing CHC, the corresponding number is 6[2].

In both cases, the number of VTE events per year is lower than the number expected in women 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**




Very 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).

[1] Incidence was estimated from the totality of the epidemiological study data by comparing the relative risks for the different products with levonorgestrel-containing combined hormonal contraceptives.

[2] Mid-point of range of 5-7 per 10,000 woman-years, based on the relative risk for combined hormonal contraceptives containing levonorgestrel versus non-use for which the risk is approximately 2.3 to 3.6.

Harmonet is contraindicated if a woman has multiple risk factors that put her at high risk of VTE (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 body mass index rises.<br><br>Particularly important to consider if other risk factors also present. |
| Prolonged immobilisation, major surgery, any surgery to the legs or pelvic area, neurosurgery, or major trauma.<br><br>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/tablet/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 unwanted pregnancy.<br><br>Antithrombotic treatment should be considered if Harmonet has not been discontinued in advance. |
| Positive family history (presence or history of VTE in a sibling or parent especially at a relatively early age e.g., before 50 years). | If a hereditary predisposition is suspected, the patient should be referred to a specialist for examination 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 age 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 during the 6-week period of the puerperium, must be considered (for additional information see section 4.6).

*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 doctor 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 feeling of warmth in the affected leg; discolouration or redness of skin

on the leg.

Symptoms of pulmonary embolism (PE) may 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 may include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye, symptoms may include painless blurring of vision, which may progress to loss of vision. Sometimes loss of vision may occur almost immediately.

Risk of arterial thromboembolism (ATE)

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

*Risk factors for arterial thromboembolism (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 which 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 combined risk is greater than the sum of the individual factors – in this case the 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 arterial thromboembolism (ATE)**

| **Risk factor** | **Comment** |
|---|---|
| Increasing age | Particularly age above 35 years |
| Smoking | Women using a CHC should be advised not to smoke. Women aged over 35 years 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 body mass index increases.<br><br>Particularly important in women with additional risk factors. |
| Positive family history (presence | If a hereditary predisposition is suspected, the |

| Risk factor | Comment |
|---|---|
| or history of arterial thromboembolism in a sibling or parent especially at a relatively early age e.g., before 50 years). | patient should be referred to a specialist for examination before deciding about any CHC use. |
| Migraine | An increase in frequency or severity of migraine (which may be prodromal of a cerebrovascular event) during CHC use may be a reason for immediate discontinuation of CHC. |
| Other medical conditions associated with adverse vascular events | Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic *lupus erythematosus* (SLE). |

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

Symptoms of a cerebrovascular accident may include:
- sudden numbness or weakness of the face, arm or leg (especially on one side of the body only)
- sudden trouble walking, dizziness, loss of balance or coordination
- sudden confusion, trouble speaking or understanding
- sudden impairment of vision in one or both eyes
- sudden, severe or prolonged headache with no known cause
- loss of consciousness or fainting with or without seizures.

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

Symptoms of myocardial infarction 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, and/or abdomen
- feeling of being full, having indigestion, or choking
- sweating, nausea, vomiting, or dizziness
- extreme weakness, anxiety, or shortness of breath
- rapid or irregular heartbeats.

***2. Genital Tumours***

Cervical cancer

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

Some studies suggest that COC use may be 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. In cases of

undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Breast cancer

A meta-analysis of 54 epidemiological studies showed that there is a slightly increased risk (relative risk coefficient 1.24) of having breast cancer diagnosed in women who are using COCs compared to never-users. The increased risk gradually disappears during the course of the 10 years after cessation of COC use. 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 due to regular clinical monitoring, the biological effects of COCs, or a combination of both. Because breast cancer is rare in women under 40 years of age, the increase in the number of breast cancer diagnoses in current and recent COC users is small in relation to the lifetime risk of breast cancer. Breast cancers diagnosed in COC users tend to be less advanced clinically than the cancers diagnosed in non-users.

***3. Hepatic Neoplasia/Liver Disease***

In very rare cases, benign hepatic tumours, and even more rarely, malignant hepatocellular tumours may be associated with COC use. The risk appears to increase with duration of COC use. Rupture of benign hepatic tumours may cause death through intra-abdominal haemorrhage.

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 are prescribed a COC, they should be carefully monitored and, if the condition recurs, the COC should be discontinued.

Hepatocellular injury has been reported with COC use. Early identification of drug-related hepatocellular injury and discontinuation of use of the tablets can decrease the severity of hepatotoxicity. If hepatocellular injury is diagnosed, patients should stop their COC use, start using a non-hormonal form of contraception and consult their doctor.

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

***4. Ocular Lesions***

With use of COCs, there have been reports of retinal vascular thrombosis, which may have led to partial or complete loss of vision. COC use should be discontinued and the cause of symptoms investigated, particularly if there are signs of the following symptoms: visual disturbance, proptosis or diplopia, papilledema, or retinal vascular lesions.

***5. Gallbladder***

According to previous studies, COC and oestrogen users have an increased lifetime relative risk of gallbladder surgery. More recent studies nevertheless suggest that the relative risk of developing a gallbladder disease is small in COC users.

***6. Blood Pressure***

Increases in blood pressure have been reported in women taking COCs. In women with a history of hypertension or hypertension-related diseases or renal disease, she should be advised to use another method of contraception. If COCs are prescribed for a hypertensive woman, she should be monitored closely and, if a significant increase in blood pressure occurs, COCs should be discontinued (see section 4.3). For most women, elevated blood pressure will return to normal after stopping COCs, and there is no difference in the occurrence of hypertension among ever- and never-users of COCs.

***7. Migraine/Headache***

The exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent or severe requires discontinuation of COCs and evaluation of the cause.

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

***8. Immune System***

Angioedema

Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired 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. The woman's blood pressure should be measured and a physical examination should be performed, taking into account contraindications (see section 4.3) and warnings (see section 4.4).*** It is important to draw the woman's attention to the information on venous and arterial thrombosis, including the risk of Harmonet compared with other CHCs, the symptoms of venous and arterial thrombosis, known risk factors and what to do in the event of a suspected thrombosis.

The woman should also be instructed to carefully read the package leaflet and to adhere to the advice given. The frequency and nature of follow-up appointments should be based on established treatment guidelines and be adapted to the individual woman's needs.

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

***2. Effects on carbohydrate and lipid metabolism***

Glucose intolerance has been reported in COC users. Women with glucose intolerance

or diabetes mellitus should be carefully monitored during COC use.

A small proportion women will experience adverse changes in lipid metabolism while taking oral contraceptives. Non-hormonal contraception should be considered in women with uncontrolled dyslipidaemias. Persistent hypertriglyceridemia may occur in a small proportion of women during COC use. Elevated plasma triglycerides may lead to pancreatitis or other complications.

A decline in serum HDL cholesterol has been reported with many progestin products. Because oestrogens increase HDL cholesterol, the overall effect of a COC depends on the balance achieved between doses of oestrogen and progestin and the nature and overall amount of progestins in the contraceptive. The amounts of both hormones should be considered in the choice of a COC.

Patients with hyperlipidaemia should be followed closely during COC use.

***3. Vaginal bleeding***

Breakthrough bleeding and spotting sometimes occurs with COC use, especially during the first three months of use. The type and dose of progestins may contribute to this. Non-hormonal causes should be considered and possible malignancy or pregnancy should be ruled out. If pathology has been excluded, continued use of the COC or switching to another product may solve the problem.

In some women, withdrawal bleeding may not occur during the tablet-free interval. When COC has been taken according to directions, the occurrence of pregnancy is unlikely. 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 non-hormonal method of contraception should be used until the possibility of pregnancy is excluded.

Some women may experience amenorrhea (possibly also anovulation) or oligo menorrhoea after discontinuation of oral contraceptives, especially when such a condition was pre-existing.

***4. Liver***

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.

***5. Depression***

If significant depression develops during COC use, the medication should be stopped and the patient switched to an alternate method of contraception in an attempt to determine whether the symptom is drug related. Individuals with a history of depression should be carefully observed during use of oral contraceptives and the drug discontinued if depression recurs.

***6. Folate levels***

Serum folate levels may be depressed by COC use. This may be of clinical significance if a woman becomes pregnant immediately after discontinuing COCs.

***7. Fluid retention***

COCs should be prescribed with caution to patients whose condition may worsen because of fluid retention.

***8. Other***

Diarrhoea and/or vomiting may reduce hormone absorption and result in decreased serum concentrations.

Herbal preparations containing St John's Wort (*Hypericum perforatum*) should not be used concomitantly with Harmonet. St. John's Wort may lower the plasma concentrations of the active substances and lead to a decreased effect (see section 4.5).

Psychiatric 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.

Excipient information

Harmonet contains lactose and sucrose. Women with rare hereditary problems of galactose or fructose intolerance, total lactase deficiency, glucose-galactose malabsorption, or sucrase-isomaltase deficiency should not take this medicine.

**4.5 Interaction with other medicinal products and other forms of interaction**

Drug-drug interactions

Interactions between ethinyloestradiol and other substances may lead to decreased or increased serum ethinyloestradiol concentrations.

Decreased serum ethinyloestradiol concentrations may increase breakthrough bleeding and menstrual irregularities and reduce efficacy of the COC.

If ethinyloestradiol and products that may lead to decreased plasma ethinyloestradiol concentrations are used concomitantly, it is recommended that a non-hormonal method of birth control (such as condoms or spermicides) be used in addition to the regular intake of Harmonet. If prolonged use of such products is necessary, COCs are not the primary contraceptive.

After discontinuation of substances that may lead to decreased ethinyloestradiol plasma concentrations, use of a non-hormonal backup method is recommended for at least 7

days. Longer use of a backup method is advisable after discontinuation of substances that have led to induction of hepatic microsomal enzymes, resulting in decreased serum ethinyloestradiol concentrations. Enzyme induction may take several weeks, depending on the dose, duration of use and rate of elimination of the inducing substance.

Examples of substances that may decrease serum ethinyloestradiol concentrations:
- Substances that reduce gastrointestinal transit time
- Substances that induce hepatic microsomal enzymes, such as rifampicin, rifabutin, barbiturates, primidone, phenylbutazone, phenytoin, dexamethasone, griseofulvin, topiramate, some protease inhibitors, and modafinil
- Ritonavir (possibly by induction of hepatic microsomal enzymes)

Examples of substances that may increase serum ethinyloestradiol concentrations:
- Atorvastatin
- Competitive inhibitors for sulfation of ethinyloestradiol in the gastrointestinal wall, such as ascorbic acid (vitamin C) and paracetamol
- Substances which inhibit cytochrome P 450 3A4 isoenzymes such as indinavir, fluconazole, and troleandomycin

Troleandomycin may increase the risk of intrahepatic cholestasis during co-administration with COCs.

Ethinyloestradiol 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).

Starting hormonal contraception in a woman who uses lamotrigine may decrease the lamotrigine level in plasma and may diminish its anticonvulsive effect. Correspondingly, discontinuation of contraception may increase the lamotrigine level in plasma.

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

Care should be exercised when tizanidine is prescribed to oral contraceptive users. Oral contraceptives containing ethinyloestradiol and gestodene increase, to a clinically significant extent, the plasma concentrations and effects of tizanidine.

Familiarize yourself with other concomitant medications to allow identification of potential interactions.

Herbal products containing St. John´s Wort (*Hypericum perforatum*) should not be used at the same time with this product as there is a potential risk for loss of the contraceptive effect. Breakthrough bleeding and unwanted pregnancies have been reported. This is because St. John´s Wort induces hepatic microsomal enzymes. This effect may last for at least two weeks after discontinuation of treatment with St. John´s Wort.

<u>Pharmacodynamic interactions</u>

In clinical trials where patients were treated for hepatitis C virus infections (HCV) with ombitasvir/paritaprevir/ritonavir and dasabuvir either with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinyloestradiol-containing medications, such as combined hormonal contraceptives (CHCs). Also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinyloestradiol-containing medications such as CHCs (see section 4.3). For this reason, patients using Harmonet should switch to another contraceptive method (e.g., progestin-only contraception or non-hormonal methods) before starting therapy with these combination drug regimens. Harmonet tablets can be restarted 2 weeks after completion of treatment with these combination drug regimens.

## 4.6 Fertility, pregnancy and lactation

This product must not be used during pregnancy.

Pregnancy

If pregnancy occurs during the treatment with COCs, their use should be discontinued. There is no conclusive evidence that the oestrogen and progestin contained in COCs will damage the developing foetus if oral contraceptives are accidentally taken in the early stages of pregnancy.

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

Breast-feeding

Breastfeeding may be influenced by COCs as they reduce the quantity and change the composition of breast milk. Use of COCs is generally not be recommended until the child has been completely weaned. Small amounts of the steroids in the oral contraceptives and/or their metabolites may pass into breast milk. Some adverse effects on the child have been reported, including jaundice and breast enlargement.

## 4.7 Effects on ability to drive and use machines

Not applicable.

## 4.8 Undesirable effects

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

- An increased risk of arterial and venous thrombotic and thromboembolic events has been observed in women using CHCs. These events include myocardial infarction, stroke, transient ischaemic attacks (TIA), venous thrombosis and pulmonary embolism. Events are described in more detail in section 4.4.
- Cervical intraepithelial neoplasia (CIN) and cervical cancer.
- Breast cancer diagnosis.
- Benign hepatic tumours (e.g., focal nodular hyperplasia, hepatic adenoma).

Other potential adverse effects in COC users:

| System organ class | 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) |
|---|---|---|---|---|
| Psychiatric disorders | Mood changes, including depression, changes in libido | | | |
| Reproductive system disorders | Change in menstrual flow, spotting/breakthrough bleedings, breast pain, breast tenderness, breast enlargement, secretion from the breast, dysmenorrhoea, changes in cervical ectropion and secretion, amenorrhea | | | |
| Nervous system disorders | Headache, including migraine, nervousness, dizziness | | Exacerbation of chorea | |
| Gastrointestinal disorders | Nausea, vomiting, abdominal pain | Abdominal cramps, bloating | Pancreatitis, ischemic colitis, hepatic adenomas, hepatocellular carcinomas, inflammatory bowel disease (frequency unknown) (Crohn´s disease, ulcerative colitis) | |
| Skin disorders | Acne | Rash, chloasma (melasma) which may be permanent, hirsutism, alopecia | Erythema nodosum, erythema multiforme | |
| Infections and infestations | Vaginitis, including candidiasis | | | |
| Neoplasms benign, malignant and unspecified | | | Hepatocellular carcinomas | |
| General disorders | Fluid retention/oedema | | | |
| Metabolism and nutrition disorders | | Changes in appetite (increase or decrease) | Glucose intolerance, exacerbation of porphyria | |
| Vascular disorders | | | Aggravation of varicose veins, venous or arterial thromboembolism | |
| Hepatobiliary disorders | | | Cholestatic jaundice, gallbladder disease, including gallstones, hepatocellular injury (frequency unknown) (e.g., | |

| System organ class | 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) |
|---|---|---|---|---|
| | | | hepatitis, hepatic function abnormal) | |
| Immune system disorders | | | Anaphylactic/anaphylactoid reactions including very rare cases of urticaria, angioedema, and severe reactions in the respiratory and circulatory system, exacerbation of systemic lupus erythematosus (SLE) | Exacerbation of symptoms of hereditary and acquired angioedema |
| Eye disorders | | | Intolerance to contact lenses, optic neuritis, retinal vascular thrombosis | |
| Renal and urinary disorders | | | Haemolytic uremic syndrome | |
| Investigations | Change in weight (increase or decrease) | Increase in blood pressure, changes in serum lipid levels, including hypertriglyceridemia | Decrease in serum folate levels | |

Optic neuritis may lead to partial or complete loss of vision.

COCs may worsen existing gallbladder disease and accelerate the development of this disease in previously asymptomatic women.

Serum folate levels may be depressed by COC therapy.

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.

### 4.9 Overdose

Symptoms of oral contraceptive overdose have been reported in adults and children. They include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue, and withdrawal bleeding. There is no antidote and the treatment is symptomatic.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and oestrogens, fixed combinations, ATC code: G03AA10.

Harmonet is a combination oral contraceptive (COC) containing ethinyloestradiol (EE) and gestodene. 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.

When taken correctly and consistently, the probability of failure of contraceptive efficacy of COCs is 0.1%. However, the probability of failure of contraceptive efficacy during typical use is 5% for all types of oral contraceptives. The efficacy of most methods of contraception depends upon the regularity of use. Failure of contraceptive efficacy is more likely if tablets are missed.

**5.2 Pharmacokinetic properties**

**Gestodene**

Absorption

After oral administration, gestodene is absorbed rapidly and completely. After oral intake of a single dose, peak plasma concentrations of approximately 2 to 4 ng/mL are reached in about 1 hour. Bioavailability is about 99%.

Distribution

Gestodene binds to serum albumin and sex hormone-binding globulin (SHBG). Only 1 to 2% of the total drug concentration in serum is in the form of a free steroid, 50 to 70% is specifically bound to SHBG.

Ethinyloestradiol-induced increases in SHBG have an effect on the binding of gestodene to serum proteins, increasing the fraction bound to SHBG and decreasing the fraction bound to albumin. The volume of distribution of gestodene is 0.7 to 1.4 l/kg.

Biotransformation

Gestodene is completely metabolised by the known steroid metabolic pathways. The average metabolic serum clearance is 0.8 to 1.0 mL/min/kg. Direct interactions have not been observed with single doses of gestodene given concomitantly with ethinyloestradiol.

Elimination

Reduction of gestodene level in serum occurs in 2 steps. In the terminal elimination phase, the half-life is typically 12 to 20 hours. Gestodene is excreted in the urine and bile (in a ratio of 6:4) in metabolised form only. The half-life of metabolite excretion is about 1 day.

Steady state

Concentration of SHBG has an effect on pharmacokinetics of gestodene; SHBG concentration increases by about 3-fold with concomitant administration of

ethinyloestradiol. In daily use, the drug concentration in serum increases by about 3 to 4-fold and steady state is reached during the second half of the treatment cycle.

**Ethinyloestradiol**

Absorption

Orally administered ethinyloestradiol is absorbed rapidly and completely.

The peak serum concentration of approximately 30 to 80 pg/mL is reached within 1 to 2 hours. Due to pre-systemic conjugation and first-pass metabolism, the absolute bioavailability is about 60%.

Distribution

Oestradiol is highly but not specifically bound to serum albumin (about 98.5%), and increases the concentration of SHBG in the serum. The apparent volume of distribution was determined to be about 5 to 18 L/kg.

Biotransformation

Ethinyloestradiol is conjugated pre-systematically both on the mucous membrane of the small intestine and in the liver. Ethinyloestradiol is mostly metabolized by aromatic hydroxylation; in this case, however, a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as glucuronide and sulfate conjugates. The metabolic clearance is approximately 5 to 13 mL/min/kg.

Elimination

Reduction of ethinyloestradiol level in serum occurs in 2 steps; in the terminal elimination phase, the half-life is typically approximately 16 to 24 hours. Ethinyloestradiol is excreted in urine and bile (in a ratio of 4:6) in metabolised form only. The half-life of metabolite excretion is about 1 day.

Steady state

Steady state is reached in 3 to 4 days and serum concentrations of the drug are 20% higher than after a single dose.

## 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Lactose, maize starch, povidone, magnesium stearate, sucrose, polyethylene glycol

6000, calcium carbonate, talc, wax E.

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf-life**

Please refer to the outer package for expiry date.

**6.4 Special precautions for storage**

Please refer to the outer package for storage condition.

Pfizer Corporation Hong Kong Limited
JUL 2024

Version approved: 12 FEB 2025