HARMONET®

1. NAME OF THE MEDICINAL PRODUCT

Harmonet®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.075 mg of gestodene and 0.02 mg of ethinylestradiol

Excipients with known effect : lactose and sucrose (each tablet contains 37.505 mg lactose hydrouse and 19.66 mg sucrose; see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablets
White, sugar coated tablets 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 combined hormonal contraceptives (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 CHCs cannot be used in the presence of one of the conditions described below. Use of Harmonet® must be interrupted immediately if one of the following conditions appears for the first time.

- 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 disease – current stroke, 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 (micro or macroangiopathy)
    - severe hypertension
    - severe dyslipoproteinaemia
  - Coronary disease

- Presence or risk of venous thromboembolism (VTE)
  - Venous thromboembolism – current VTE (on anticoagulants) or history of VTE (eg. deep venous thrombosis [DVT] or pulmonary embolism [PE])
  - 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)
- Thrombogenic valvulopathy;
- Thrombogenic arrhythmias;
- Suspected or confirmed breast cancer;
- Suspected or confirmed oestrogen-sensitive neoplasms (endometrial etc.);
- Hepatic adenoma or carcinoma;
- Severe hepatic disorders - until hepatic function has normalised;
- Abnormal vaginal bleeding of unknown cause;
- Suspected or confirmed pregnancy;
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

- Pancreatitis associated with severe hypertriglyceridemia (current or history).

Harmonet® is contraindicated for concomitant use with the medicinal products containing ombitasvir/ paritaprevir/ritonavir and/or dasabuvir or medicinal products containing glecaprevir/pibrentasvir (see sections 4.4 and 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 woman should be advised to contact her doctor to determine whether the use of Harmonet® should be discontinued.

Risk of venous thromboembolism (VTE)

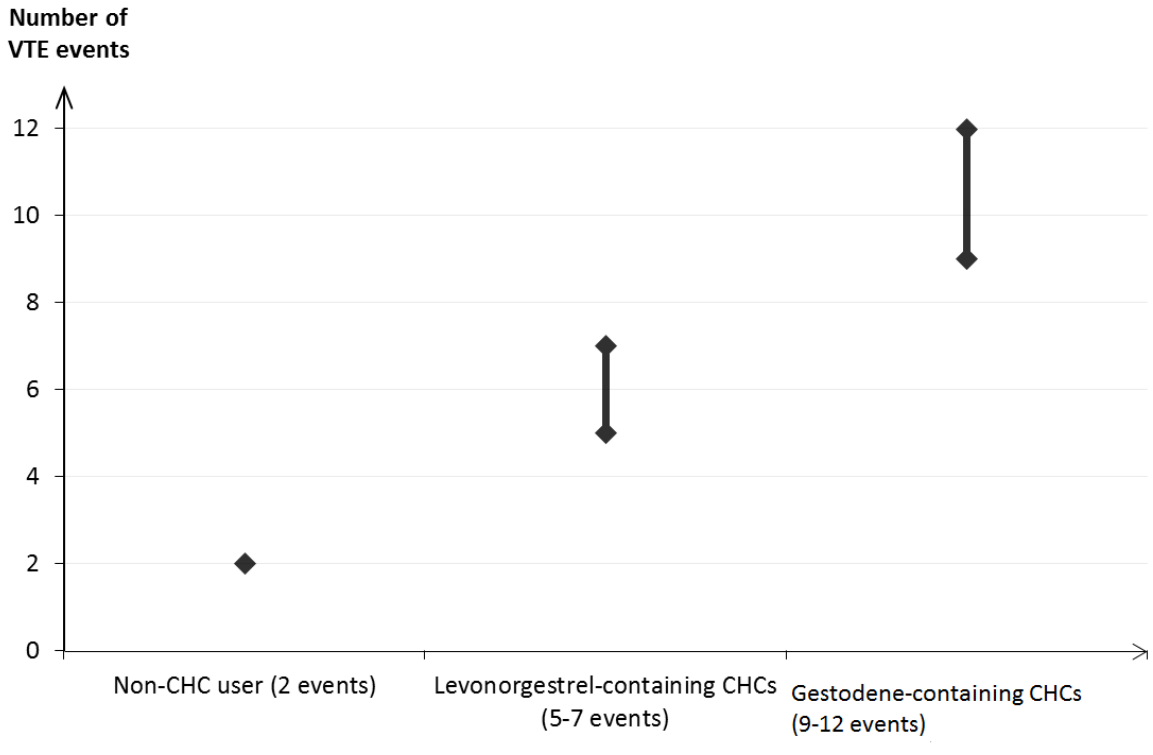
The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as Harmonet® may have up to twice this level 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 estimated[1] that out of 10,000 women who use a CHC containing gestodene between 9 and 12 women will develop a VTE in one year; this compares with about 6[2] 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.

[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 reative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6.

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



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. For information concerning vascular thrombosis of the retina, see paragraph "Ocular lesions".

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/m²)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation including air travel >4 hours can also	In these situations it is advisable to discontinue use of the pill (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.

be a risk factor for VTE, particularly in women with other risk factors	
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age eg. 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. Harmonet® cannot be started until the 28th day after a delivery (for users who choose not to breast-feed) or after an abortion or miscarriage in the second trimester (for information on "Pregnancy and lactation" 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 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 (eg 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 eg. 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 with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia, systemic lupus erythematosus and coronary disorders

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.

Gynaecological cancers

Published data do not demonstrate a causal relationship with the use of oral contraceptives whose benefits appear higher than the risks. However, all women who use this type of product should be kept under close medical supervision. If unexpected vaginal bleeding occurs, the necessary diagnostic measures should be taken to exclude a pregnancy, a malignant tumour or other possible causes.

Breast cancer
Established risk factors for the development of breast cancer include increasing age, family history, obesity, nulliparity, and late age for first full-term pregnancy.
A meta-analysis from 54 epidemiological studies reported that there is a slightly increased risk (RR=1.24) of having breast cancer diagnosed in users of oral CHCs (Collaborative Group on Hormonal Factors in Breast Cancer, Lancet 347 : 1713-1727, 1996). The observed risk decreases and progressively disappears during the 10 years following discontinuation of use of an oral CHC. Since the number of cases of breast cancer in women under 40 years of age is low, the observed increase in this number of breast cancer in users of oral CHCs (whether former or new users) nevertheless remains small in relation to the global risk of appearance of breast cancer during the lifetime of each woman. However, women presenting with nodules in the breast, fibrocystic disease or abnormal images in the mammogram should be followed particularly closely.

Cancer of the uterus
The most important risk factor for cervical cancer is persistent human papillomavirus infection.
Some studies suggest that the use of an estrogen/progestogen contraception for a long period can be associated with an elevated risk of intraepithelial or invasive cervical cancer in some populations of women. However, the precise cause of these observations has not been established and sexual behaviour or other factors such as the involvement of the human papilloma virus (HPV) could be cited to explain these observations. In cases of undiagnosed genital bleeding, adequate diagnostic measures are indicated.

Hepatic tumours and diseases
In very rare cases, benign hepatic tumours such as hepatic adenoma - and in even rarer cases, malignant hepatic tumours such as hepatocellular carcinoma - have been reported in oral CHC users. The risk of developing a tumour increases with the duration of treatment. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhage.

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

Hepatocellular injury has been reported with oral 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 oral CHC, use a non-hormonal form of contraception and consult their doctor.

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

Headaches and migraine
The occurrence or aggravation of a migraine or the development of a new type of recurrent persistent or severe headache requires the immediate discontinuation of treatment and a search for the cause. Users suffering from migraine (particularly those with aura) under treatment with oral CHCs can present a higher risk of developing a cerebrovascular accident (see section 4.3).

Ocular lesions
Cases of retinal vascular thrombosis capable of causing partial or complete blindness have been associated with usage of oral CHCs. The use of oral CHCs must be discontinued immediately if one of the following phenomena occur:
- painless blurred vision
- inexplicable loss of sight, gradual or sudden, partial or complete;
- proptosis or diplopia;
- papillary oedema;
- signs of retinal vascular lesions or optic neuritis.

In these cases, the necessary diagnostic and therapeutic measures must be taken.

Hypertension
A rise in arterial blood pressure has been reported in some users of oral CHCs. Another method of contraception should be used in women with hypertension, a history of hypertension or a hypertension based on a pathology (including certain renal pathologies). If an oral CHC is used in these patients, close medical monitoring is recommended and use of the contraceptive should be stopped if there is a significant increase in blood pressure.

Oral CHCs are contraindicated in patients with uncontrolled hypertension (see section 4.3).

Genital bleeding or absence of menstruation
In some women withdrawal bleeding may not occur during the tablet-free interval. If the oral CHC 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 excluded before continuing the use of oral CHCs and a nonhormonal back-up method of contraception should be used until the possibility of pregnancy is excluded.

Metrorrhagia and/or intercurrent blood loss (spotting) sometimes occurs, especially during the first three months that the tablets are taken. Hence any irregular bleeding does not need require investigation before an adaptation period of about three cycles.
If metrorrhagia and/or spotting are persistent, occur at irregular intervals during several successive cycles, or for the first time after prolonged use of Harmonet®, a possible organic cause should be investigated. Suitable diagnostic measures should be taken to exclude a pregnancy or tumour.

Once a pathological cause has been excluded, the problem of metrorrhagia may be solved by the continuation of the use of Harmonet® or a switch to another hormonal contraceptive. However, due to the increased risk of thromboembolic diseases, great caution is necessary when considering a switch to a pill containing a higher dose of oestrogen.

Some women can present with oligomenorrhoea or amenorrhoea (possibly accompanied by anovulation) after ending oral contraceptives, especially if these problems were already present before treatment was started. These phenomena generally stop spontaneously. If they are prolonged, it may be necessary to investigate a possible pineal gland pathology.

Depression
Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Women with a history of depression should be closely monitored. If a serious depression develops during use of Harmonet®, the treatment should be stopped and another method of contraceptive should be used to determine the causality of Harmonet®.

Immunity
Angio-edema
Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in women with a hereditary angioedema.

Glucose and lipid metabolism
Glucose intolerance has been reported in users of oral CHCs. Users of oral CHCs who have glucose intolerance or suffer from diabetes mellitus should be closely monitored.

Women under oral contraceptives who are being treated for hyperlipidaemia (hypertriglyceridaemia, hypercholesterolaemia) should be closely monitored. A small portion of women will have adverse lipid changes while taking oral CHCs. Use of an additional non-hormonal, mechanical method of contraception is recommended in women with uncontrolled dyslipidemias. Persistent hypertriglyceridaemia can occur in a low proportion of oral CHC users. Elevations of plasma triglycerides in oral CHC users may lead to pancreatitis and other complications. If the hypertriglyceridaemia cannot be controlled, a non-hormonal method of contraception should be considered.

Other warnings

If one of the following situations occurs, treatment with Harmonet® must be stopped immediately:

- acute disorders of hearing or other sensory disorders;
- at the first symptoms of thrombophlebitis or thromboembolic disease;
- at the onset of cholestatic jaundice, anicteric hepatitis or generalised pruritus;
- an increase in number of epileptic seizures.

Particular attention should be paid to users :

- presenting with benign breast tumours;
- presenting with **uterine dystrophies** (hyperplasia, fibromas);
- presenting with **hyperprolactinaemia** with or without galactorrhoea;
- with a history or current pathology known to be associated with, or which can worsen during pregnancy or the usage of oral CHCs: epilepsy, otosclerosis, asthma, varicose veins, gestational herpes, gallstones, systemic lupus erythematosis, hepatic, cardiac or renal dysfunction, chorea, haemolytic uraemic syndrome.

If contraception fails, **an ectopic pregnancy** can occur just as easily as **an intra-uterine pregnancy**.

If **chloasma/melasma** appears during a pregnancy or under oral CHCs, exposure to sunlight should be avoided.

Diarrhoea and **vomiting** can reduce the intestinal absorption of oral CHCs (see section 4.2).

Use of oral contraceptives can affect the normal metabolism of **tryptophan**, which in turn can cause a relative deficiency of pyridoxine. However, the clinical relevance of this is not yet known.

Serum levels of **folates** can be reduced by the use of oral CHCs. Users who become pregnant shortly after ending oral contraceptive treatment run an increased risk of developing folate deficiency with its associated complications.

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

Medical examination/consultation

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 (an examination of the breasts, liver, extremities and pelvic organs, including cervical cytology) should be performed, guided by the contra-indications (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.

For every combination of estrogens/progestogens, the treatment prescribed should contain the lowest possible dosage of estrogens/progestogens compatible with a low risk of failure and the needs of the user.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

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

Laboratory tests
The use of oral CHCs may cause certain physiologic changes that may be reflected in the results of certain laboratory tests, including:

- biochemical parameters of liver function (including a decrease in bilirubin and alkaline phosphatase), thyroid function (increased total T3 and T4 due to increased TBG, decreased free T3-resin uptake), adrenal function (increased plasma cortisol, increased cortisol binding globulin, decreased dehydroepiandrosterone sulphate (DHEAS), and renal function (increased plasma creatinine levels and creatinine clearance)
- plasma levels of (carrier) proteins, such as corticosteroid-binding globulin and lipid/lipoprotein fractions
- parameters of carbohydrate metabolism
- parameters of coagulation and fibrinolysis
- decreased serum folate levels

Oral contraceptives can give false positive results during the evaluation of neutrophilic alkaline phosphatase activity in the early diagnosis of pregnancy.

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

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

Interactions between ethinyloestradiol and other drugs can cause a decrease or increase in plasma levels of ethinyloestradiol.

The decrease in plasma levels of ethinyloestradiol can increase the incidence of intermenstrual bleeding and menstrual irregularities and may reduce the efficacy of the oral contraceptive. During concomitant use of substances that may lead to decreased ethyniestradiol serum concentrations, it is recommended that an additional non-hormonal, mechanical method of contraception (condoms, spermicides etc.) be used. Another method of contraception should be considered in the case of prolonged usage of these drugs.

After the discontinuation of drugs capable of reducing serum concentrations of ethinyloestradiol, it is recommended that an additional non-hormonal, mechanical method of contraception (condoms, spermicides etc.) be used for at least seven days. In the case of treatment with hepatic enzyme inducers, these measures must be observed for longer. It can actually take several weeks until the induction of enzymes has completely stopped, depending on the dose administered, the duration of treatment and the levels of elimination of the inducer.

Contraindicated association
An interaction has been observed between oral contraceptives and **St. John's Wort** (Hypericum perforatum). This interaction is probably due to an induction of certain cytochrome P450 isoenzymes by Hypericum perforatum. St. John's Wort (Hypericum perforatum) should therefore not be used at the same time as oral contraceptives.

Non-recommended associations
Decrease in plasma levels of ethinylestradiol:
- any drug capable of reducing gastrointestinal transit time.
- enzyme inducers: anticonvulsants (barbiturates, phenytoin, primidone, carbamazepine, topiramate, felbamate), dexamethasone, phenylbutazone, rifabutin, rifampicin, griseofulvin. Reduction in contraceptive efficacy through an increase in hepatic metabolism during treatment and one cycle after ending treatment.
- ritonavir (probably by induction of hepatic enzymes)
- modafinil: risk of reduction in contraceptive efficacy during treatment and one cycle after ending treatment with modafinil.
- Probably also oxcarbazepine and nevirapine

Increase in plasma levels of ethinylestradiol:
- atorvastatin
- ascorbic acid and paracetamol
- drugs that inhibit cytochrome P450 3A4 isoenzymes such as indinavir, fluconazole, voriconazole, troleandomycin (which can increase the risk of intrahepatic cholestasis during concomitant administration of oral CHCs), ketoconazole and itraconazole.

Others
Oral antidiabetic or insulin requirements can be modified by the effect of oral contraceptives on glucose tolerance.

Oral contraceptives can influence the metabolism of other drugs by inhibiting hepatic microsomal enzymes, or by inducing hepatic drug conjugation, particularly glucuronidation or by other mechanisms. Tissue or plasma concentrations of these drugs may be reduced (e.g. lamotrigine, levothyroxine, valproate) or increased (for example theophylline, ciclosporin, corticosteroids, oral anticoagulants), but the clinical significance is not always clear.

In patients treated with flunarizine: risk of galactorrhoea through the flunarizine-induced increase in sensitivity of breast tissue to prolactin.

The Summary of Product Characteristics (section "Interactions") should be consulted for all concomitant medication.

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

4.6. Fertility, pregnancy and lactation

Pregnancy
Pregnancy must be excluded before starting contraceptive treatment.

If a pregnancy is suspected, use of oral contraceptive must be stopped immediately.

There is no conclusive evidence that the estrogen and progestin contained in the oral CHC will damage the developing child if conception accidentally occurs during oral CHC use (see section 4.3)

From a clinical viewpoint, unlike diethylstilbestrol, the currently available results of numerous epidemiological studies enable a risk of malformation with estrogens administered alone or in association at the start of pregnancy to be excluded. As a result, the discovery of a pregnancy under estrogen/progestogen treatment does not justify an abortion.

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

Breastfeeding
Use of Harmonet® during lactation can cause a reduction in milk production and modify its composition. Small quantities of hormonal contraceptives and/or their metabolites have been found in breast milk and some undesirable effects have been reported in the baby, notably jaundice and a swelling of the chest. The use of oral CHCs is generally not recommended until the nursing mother has completely weaned her child. If the woman wishes to breast feed, another method of contraception should be suggested.

4.7. Effects on ability to drive and use machines

Harmonet® has not been studied in relation to the effects on the ability to drive or use machines.

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.

Use of oral CHCs is also associated with an increased risk of:
- intraepithelial cervical neoplasia and cervical cancer;
- diagnosis of breast cancer;
- benign hepatic tumors (eg. Focal nodular hyperplasia, hepatic adenomas)

See also section 4.4.

The following undesirable effects are listed by frequency grouping as follows:
Very common ≥ 1/10
Common ≥ 1/100, < 1/10
Uncommon ≥ 1/1000, < 1/100
Rare ≥ 1/10000, < 1/1000
Very rare < 1/10000
Not known (cannot be estimated from the available data)

System/target organ	Undesirable effect
Infections and infestations Common	Vaginitis including vaginal candidiasis
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Very rare	Hepatocellular carcinoma
Immune system disorders Rare	Anaphylactic, anaphylactoid reactions, including very rare

	cases of urticaria, angio-oedema, severe respiratory and circulatory disorders
Very rare	Exacerbation of systemic lupus erythematosus
Metabolism and nutrition disorders	
Uncommon	Increase or decrease in appetite
Rare	Glucose intolerance
Very rare	Exacerbation of porphyria
Psychiatric disorders	
Common	Changes in mood and libido, depression
Nervous system disorders	
Very common	Headache, migraine
Common	Nervousness, dizziness
Very rare	Exacerbation of chorea

Eye disorders	
Rare	Intolerance of contact lenses
Very rare	Optic neuritis*
Vascular disorders	
Rare	Venous thromboembolism (VTE), arterial thromboembolism (ATE)
Very rare	Thrombosis in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries Aggravation of varicose veins
Gastrointestinal disorders	
Common	Nausea, vomiting, abdominal pain
Uncommon	Abdominal cramps, bloating
Very rare	Pancreatitis, ischemic colitis
Not known	Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
Hepatobiliary disorders	
Rare	Cholestatic jaundice
Very rare	Gallstones, cholestasis**
Not known	Hepatocellular injury (eg. Hepatitis, hepatic function abnormal)
Skin and subcutaneous tissue disorders	
Common	Acne
Uncommon	Rash, chloasma, possibly persistent, hirsutism, alopecia.
Rare	Nodular erythema.
Very rare	Erythema multiforme
Renal and urinary disorders	
Very rare	Uraemic haemolytic syndrome
Reproductive system and breast disorders	
Very common	Withdrawal bleeding/spotting
Common	Pain and tenderness of the breasts, increase in volume and secretions; dysmenorrhoea; change in vaginal secretions and menstruation, amenorrhoea, uterine ectropion
General disorders and administration site conditions	
Common	Fluid retention, oedema
Investigations	
Common	increase or decrease in body weight
Uncommon	Arterial hypertension, change in plasma lipid levels, hypertriglyceridaemia
Rare	Reduction in serum folate levels***

* Optic neuritis can cause partial or total blindness.

** Oral CHCs can exacerbate an existing disorder of the gallbladder or activate the development of such a disorder in asymptomatic users.

*** Serum folate levels can be reduced under oral CHCs. This can be of clinical significance if the user rapidly falls pregnant after stopping the pill.

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. Any suspected

adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9. Overdose

Symptoms
The symptoms of overdosage in adults and children are as follows: nausea, vomiting, dizziness, abdominal pain, somnolence, fatigue. In the user, withdrawal bleeding and breast tenderness can occur.

Treatment
There is no specific antidote and any treatment should depend on the symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: Estrogen-progestin fixed combination. ATC-code: G03AA10

Mechanism of action
Harmonet® suppresses gonadotropins in a manner that inhibits ovulation, which leads to contraception. The resulting contraceptive effect of CHCs is based on various mechanisms, the most important of which is the inhibition of ovulation.

5.2. Pharmacokinetic properties

Gestodene is rapidly and completely absorbed; it is subject to minimal first-pass metabolism, and is completely bioavailable after oral administration. The elimination half-life for gestodene is approximately 13 hours after a single oral dose. After repeated oral doses of 75 µg gestodene + 20 µg of ethinylestradiol, the elimination half-life is prolonged to approximately 20 hours.
In the plasma, gesodene is almost exclusively bound to proteins, and only a minor fraction is present in its free form. The increase of SHBG on the one hand, and the high binding affinity of gestodene to this protein on the other, are mainly responsible for the accumulation of the drug in the plasma as well as for the prolongation of its elimination half-life. Gestodene is metabolized mainly by reduction of the 3-ceto group and the double D4 binding, as well as by certain steps of hydroxylation. The metabolites of gestodene are excreted with urine (50%) and feces (33%) with an elimination half-life of about 1 day.

Ethinylestradiol is rapidly and completely absorbed after oral administration. Due to an extensive first-pass metabolism, the mean bioavailability of ethinylestradiol is about 40-60%, with marked interindividual variation. Following repeated oral administration, the plasma levels of ethinylestradiol increase by about 25-50%, reaching a steady state during the second half of each treatment cycle. Ethinylestradiol is highly bound to albumin (ca. 98%) but not to SHBG. Ethinylestradiol is excreted in the form of metabolites. About 40% is excreted in the urine and about 60% with the feces. The half-life of renal excretion of ethinylestradiol is about 28 hours.

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

lactose hydrouse, sucrose, maize starch, calcium carbonate, talc, polyethylene glycol 6000, povidone k-25, magnesium stearate, povidone k-90 and
wax E pharma.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Store in a dry place, below 25°C. Keep the blister in the carton package or in the carrying carton case in order to protect from light.

6.5. Nature and contents of container

21 White tablets in blister pack (PVC/Aluminium)

The pack sizes are 1X21 and 3X21.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. LICENSE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Hertzliya Pituach 46725

8. LICENSE NUMBER

121-88-30272

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