1. NAME OF THE MEDICINAL PRODUCT

EVRA transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 cm^2 transdermal patch contains 6 mg norelgestromin (NGMN) and 600 micrograms ethinyl estradiol (EE).

Each transdermal patch releases an average of 203 micrograms of NGMN and 33.9 micrograms of EE per 24 hours. Medicinal product exposure is more appropriately characterised by the pharmacokinetic profile (see section 5.2).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.

Thin, matrix-type transdermal patch consisting of three layers.

The outside of the backing layer is beige matte color

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Female contraception

EVRA is intended for women of fertile age.
The safety and efficacy has been established in women aged 18 to 45 years.

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

4.2 Posology and method of administration

Posology
To achieve maximum contraceptive effectiveness, patients must be advised to use EVRA exactly as directed. For initiation instructions see 'How to start EVRA' below.

Only one transdermal patch is to be worn at a time.

Each used transdermal patch is removed and immediately replaced with a new one on the same day of the week (Change Day) on Day 8 and Day 15 of the cycle. Transdermal patch changes may occur at any time on the scheduled Change Day. The fourth week is transdermal patch-free starting on Day 22.

A new contraceptive cycle begins on the next day following transdermal patch-free week; the next EVRA transdermal patch should be applied even if there has been no withdrawal bleeding or if withdrawal bleeding has not yet stopped.

Under no circumstances should there be more than a 7-day transdermal patch-free interval between dosing cycles. If there are more than 7 transdermal patch-free days, the user may not be protected against pregnancy. A non-hormonal contraceptive must then be used concurrently for 7 days. The risk of

ovulation increases with each day beyond the recommended contraceptive-free period. If intercourse has occurred during such an extended transdermal patch-free interval, the possibility of pregnancy should be considered.

Special populations

Body weight equal or greater than 90 kg
Contraceptive efficacy may be decreased in women weighing equal or greater than 90 kg.

Renal impairment
EVRA has not been studied in women with renal impairment. No dose adjustment is necessary but as there is a suggestion in the literature that the unbound fraction of ethinyl estradiol is higher, EVRA should be used with supervision in this population.

Hepatic impairment
EVRA has not been studied in women with hepatic impairment. EVRA is contraindicated in women with hepatic impairment (see section 4.3).

Post-menopausal women
EVRA is not indicated for post-menopausal women and is not intended for use as hormonal replacement therapy.

Paediatric population
Safety and efficacy have not been established in adolescents under 18 years of age. There is no relevant use of EVRA in children and pre-menarchal adolescents.

Method of administration
EVRA should be applied to clean, dry, hairless, intact healthy skin on the buttock, abdomen, upper outer arm or upper torso, in a place where it will not be rubbed by tight clothing. EVRA should not be placed on the breasts or on skin that is red, irritated or cut. Each consecutive transdermal patch should be applied to a different place on the skin to help avoid potential irritation, although they may be kept within the same anatomic site.

The transdermal patch should be pressed down firmly until the edges stick well.

To prevent interference with the adhesive properties of the transdermal patch, no make-up, creams, lotions, powders or other topical products should be applied to the skin area where the transdermal patch is placed or where it will be applied shortly.

It is recommended that users visually check their transdermal patch daily to ensure continued proper adhesion.

The EVRA transdermal patch should not be cut, damaged or altered in any way as this may compromise contraceptive effectiveness.

Used transdermal patches should be discarded carefully in accordance with the instructions given in section 6.5.

How to start EVRA

When there has been no hormonal contraceptive use in the preceding cycle
Contraception with EVRA begins on the first day of menses. A single transdermal patch is applied and worn for one full week (7 days). The day the first transdermal patch is applied (Day 1/Start Day) determines the subsequent Change Days. The transdermal patch Change Day will be on this day every week (cycle Days 8, 15, 22 and Day 1 of the next cycle). The fourth week is transdermal patch-free starting on Day 22.

If Cycle 1 therapy starts after first day of the menstrual cycle, a non-hormonal contraceptive should be used concurrently for the first 7 consecutive days of the first treatment cycle only.

When switching from an oral combined contraceptive
Treatment with EVRA should begin on the first day of withdrawal bleeding. If there is no withdrawal bleeding within 5 days of the last active (hormone containing) tablet, pregnancy must be ruled out prior to the start of treatment with EVRA. If therapy starts after the first day of withdrawal bleeding, a non-hormonal contraceptive must be used concurrently for 7 days.

If more than 7 days elapse after taking the last active oral contraceptive tablet, the woman may have ovulated and should, therefore, be advised to consult a physician before initiating treatment with EVRA. If intercourse has occurred during such an extended pill-free interval, the possibility of pregnancy should be considered.

When changing from a progestogen-only-method
The woman may switch any day from the progestogen-only pill (from an implant on the day of its removal, from an injectable when the next injection would be due), but a back-up barrier method of birth control must be used during the first 7 days.

Following abortion or miscarriage
After an abortion or miscarriage that occurs before 20 weeks gestation, EVRA may be started immediately. An additional method of contraception is not needed if EVRA is started immediately. Be advised that ovulation may occur within 10 days of an abortion or miscarriage.

After an abortion or miscarriage that occurs at or after 20 weeks gestation, EVRA may be started either on Day 21 post-abortion or on the first day of the first spontaneous menstruation, whichever comes first. The incidence of ovulation on Day 21 post abortion (at 20 weeks gestation) is not known.

Following delivery
Users who choose not to breast-feed should start contraceptive therapy with EVRA no sooner than 4 weeks after child-birth. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of EVRA or the woman has to wait for her first menstrual period.

For breast-feeding women, see section 4.6.

<u>What to do if the transdermal patch comes off or partly detaches</u>
If the EVRA transdermal patch partly or completely detaches and remains detached, insufficient medicinal product delivery occurs.

If EVRA remains even partly detached:

- for less than one day (up to 24 hours): it should be re-applied to the same place or replaced with a new EVRA transdermal patch immediately. No additional contraceptive is needed. The next EVRA transdermal patch should be applied on the usual "Change Day".
- for more than one day (24 hours or more) or if the user is not aware when the transdermal patch has lifted or become detached: the user may not be protected from pregnancy: The user should stop the current contraceptive cycle and start a new cycle immediately by applying a new EVRA transdermal patch. There is now a new "Day 1" and a new "Change Day". A non-hormonal contraceptive must be used concurrently for the first 7 days of the new cycle only.

A transdermal patch should not be re-applied if it is no longer sticky; a new transdermal patch should be applied immediately. Supplemental adhesives or bandages should not be used to hold the EVRA transdermal patch in place.

<u>If subsequent EVRA transdermal patch change days are delayed</u>

At the start of any transdermal patch cycle (Week One/Day 1):
The user may not be protected from pregnancy. The user should apply the first transdermal patch of the new cycle as soon as remembered. There is now a new transdermal patch "Change Day" and a new "Day 1". A non-hormonal contraceptive must be used concurrently for the first 7 days of the new cycle. If intercourse has occurred during such an extended transdermal patch-free interval, the possibility of pregnancy should be considered.

In the middle of the cycle (Week Two/Day 8 or Week Three/Day 15):
- for one or two days (up to 48 hours): The user should apply a new EVRA transdermal patch immediately. The next EVRA transdermal patch should be applied on the usual "Change Day". If during the 7 days preceding the first skipped day of transdermal patch application, the transdermal patch was worn correctly, no additional contraceptive use is required.
- for more than two days (48 hours or more): The user may not be protected from pregnancy. The user should stop the current contraceptive cycle and start a new four-week cycle immediately by putting on a new EVRA transdermal patch. There is now a new "Day 1" and a new "Change Day". A non-hormonal contraceptive must be used concurrently for the first 7 consecutive days of the new cycle.

At the end of the cycle (Week Four/Day 22):
- If the EVRA transdermal patch is not removed at the beginning of Week 4 (Day 22), it should be removed as soon as possible. The next cycle should begin on the usual "Change Day", which is the day after Day 28. No additional contraceptive use is required.

<u>Change day adjustment</u>
In order to postpone a menstrual period for one cycle, the woman must apply another transdermal patch at the beginning of Week 4 (Day 22) thus not observing the transdermal patch free interval. Breakthrough bleeding or spotting may occur. After 6 consecutive weeks of transdermal patch wear, there should be a transdermal patch free interval of 7 days. Following this, the regular application of EVRA is resumed.

If the user wishes to move the Change Day the current cycle should be completed, removing the third EVRA transdermal patch on the correct day. During the transdermal patch-free week a new Change Day may be selected by applying the first EVRA transdermal patch of the next cycle on the first occurrence of the desired day. In no case should there be more than 7 consecutive transdermal patch-free days. The shorter the transdermal patch-free interval, the higher the risk that the user does not have a withdrawal bleed and may experience breakthrough bleeding and spotting during the subsequent treatment cycle.

In case of minor skin irritation

If transdermal patch use results in uncomfortable irritation, a new transdermal patch may be applied to a new location until the next Change Day. Only one transdermal patch should be worn at a time.

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following conditions. If one of these disorders occurs during the use of EVRA, EVRA must be discontinued immediately.

- Presence or risk of venous thromboembolism (VTE)
  - Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. 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);
- 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
    - severe hypertension
    - severe dyslipoproteinaemia
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected oestrogen-dependent neoplasia
- Abnormal liver function related to acute or chronic hepatocellular disease
- Hepatic adenomas or carcinomas
- Undiagnosed abnormal genital bleeding
- Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Warnings

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

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

There is no clinical evidence indicating that a transdermal patch is, in any aspect, safer than combined oral contraceptives.

EVRA is not indicated during pregnancy (see section 4.6).

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 EVRA 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 EVRA, 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.

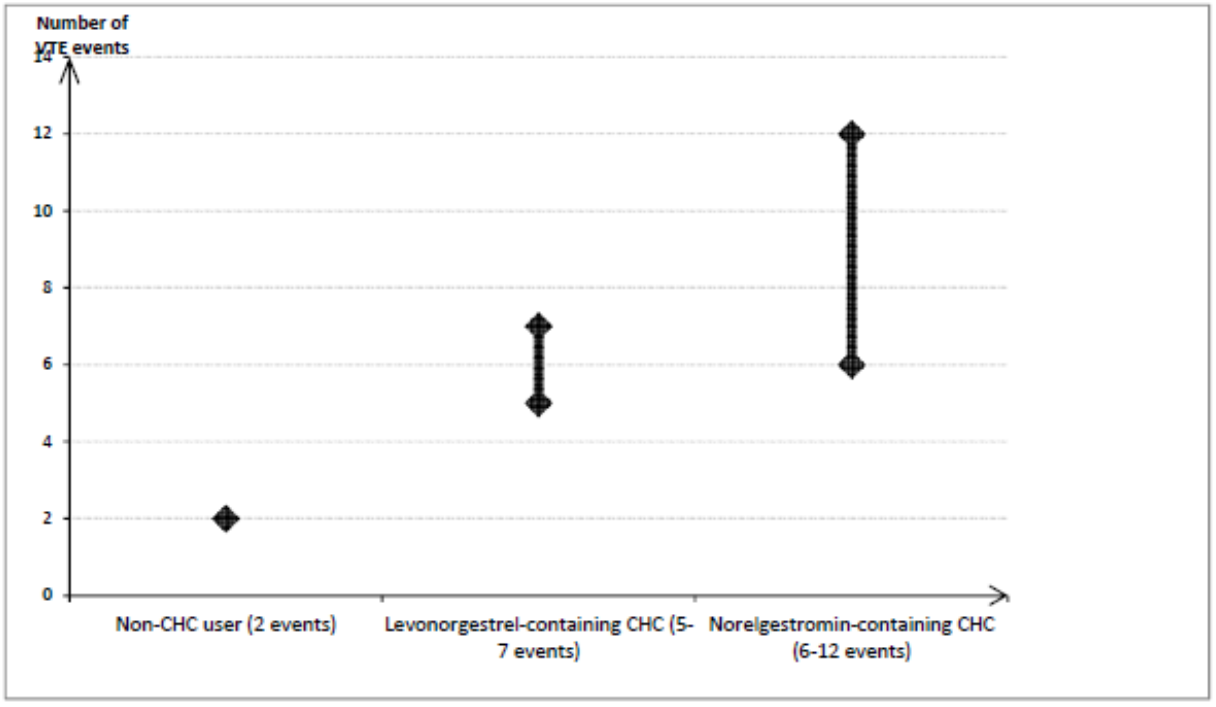
In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

It is estimated that out of 10,000 women who use a low dose CHC that contains levonorgestrel, about 6[1] will develop a VTE in one year. Studies have suggested that the incidence of VTE in women who used EVRA is up to 2-fold higher than in users of CHCs that contain levonorgestrel. This corresponds to between about 6 and 12 VTEs in a year out of 10,000 women who use EVRA.

In both cases, the number of VTEs per year is fewer 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



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.

[1] 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

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).

EVRA 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 be a risk factor for VTE, particularly in women with other risk factors	In these situations it is advisable to discontinue the use of the patch (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 EVRA has not been discontinued in advance
Positive family history (venous thromboembolism ever in a sibling or parent at relatively early age)	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any 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).

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 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). EVRA 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 rises. Particularly important in women with additional risk factors
Positive family history (arterial thromboembolism ever in a sibling or parent 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 with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia, systemic lupus erythematosus.

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 myocardial infarction (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.

Women using combined contraceptives should be emphatically advised to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, hormonal contraceptive use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy (coumarins).

Tumours

An increased risk of cervical cancer in long-term users of COCs has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

A meta-analysis of 54 epidemiological studies reported that there is a slightly increased risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. Therefore a hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women using EVRA.

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 ethinyl estradiol-containing medications such as combined hormonal contraceptives (CHCs) (see sections 4.3 and 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.

Other conditions

- Contraceptive efficacy may be reduced in women weighing equal or greater than 90 kg (see sections 4.2 and 5.1).
- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using combined hormonal contraceptives.
- Although small increases of blood pressure have been reported in many women using hormonal contraceptives, clinically relevant increases are rare. A definitive relationship between hormonal

contraceptive use and clinical hypertension has not been established. If, during the use of combined hormonal contraceptives in pre-existing hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the combined hormonal contraceptive must be withdrawn.

Combined hormonal contraceptive use may be resumed if normotensive values can be achieved with antihypertensive therapy.

- The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: Jaundice and/or pruritus related to cholestasis; gallbladder disease including cholecystitis and cholelithiasis; porphyria; systemic lupus erythematosus; haemolytic ureamic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of combined hormonal contraceptives until markers of liver function return to normal. Recurrence of cholestatic-related pruritus, which occurred during a previous pregnancy or previous use of sex steroids necessitates the discontinuation of combined hormonal contraceptives.
- Although combined hormonal contraceptives may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetes during use of combined hormonal contraceptives. However, diabetic women should be carefully observed, particularly in the early stage of EVRA use.
- Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC use.
- Chloasma may occasionally occur with the use of hormonal contraception, especially in users with a history of chloasma gravidarum. Users with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while using EVRA. Chloasma is often not fully reversible.

Medical examination/consultation

Prior to the initiation or reinstitution of EVRA a complete medical history (including family history) should be taken and pregnancy should be ruled out. Blood pressure should be measured and a physical examination should be performed guided by the contra-indications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of EVRA 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.

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

Bleeding irregularities

With all combined hormonal contraceptives, irregular blood loss (spotting or breakthrough bleeding) can occur, especially during the initial months of usage. For this reason, a medical opinion on irregular blood loss will only be useful after an adjustment period of approximately three cycles. If breakthrough bleeding persists, or breakthrough bleeding occurs after previously regular cycles, while EVRA has been used according to the recommended regimen, a cause other than EVRA should be considered. Non-hormonal causes should be considered and, if necessary, adequate diagnostic measures taken to rule out organic disease or pregnancy. This may include curettage. In some women withdrawal bleeding may not occur during this transdermal patch free period. If EVRA has been taken according to the directions described in section 4.2, it is unlikely that the woman is pregnant. However, if EVRA has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before EVRA use is continued.

Some users may experience amenorrhoea or oligomenorrhoea after discontinuing hormonal contraception, especially when such a condition was pre-existent.

4.5 Interaction with other medicinal products and other forms of interaction

Note: The prescribing information of concomitant medicinal products should be consulted to identify potential interactions.

Pharmacodynamic interactions
Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see sections 4.3 and 4.4). Therefore, EVRA-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. EVRA can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Effects of other medicinal products on EVRA
Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature**.**

Substances increasing the clearance of CHCs (diminished efficacy of CHCs by enzyme-induction),e.g.:
Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, modafinil and HIV medications ritonavir, nevirapine and efavirenz; and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (hypericum perforatum).

Management
Enzyme induction may be observed after a few days of treatment. Maximal enzyme induction is generally seen in about 10 days but may then be sustained for at least 4 weeks after the cessation of medicinal product therapy.

Short-term
A woman on short-term treatment with medicinal products that induce hepatic drug metabolising enzymes or individual active substances that induce these enzymes should temporarily use a barrier method in addition to EVRA, i.e. during the time of concomitant medicinal product administration and for 28 days after their discontinuation.

If concomitant medicinal product administration extends beyond the end of the three-week patch period, the next transdermal patch should be applied without the usual transdermal patch-free interval.

Long-term
In women on long-term treatment with enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

Substances with variable effects on the clearance of CHCs
When co-administered with CHCs, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of estrogen or progestins. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Inhibition of ethinyl estradiol metabolism
Etoricoxib has been shown to increase plasma levels of ethinyl estradiol (50 to 60%) when taken concomitantly with an oral triphasic hormonal contraceptive. It is thought that etoricoxib increases ethinyl estradiol levels because it inhibits sulfotransferase activity thereby inhibiting ethinyl estradiol metabolism.

Effect of EVRA on other medicinal products
Hormonal contraceptives may affect the metabolism of certain other active substances. Accordingly, plasma and tissue concentrations may increase (e.g. ciclosporin). Dosage adjustment of the concomitant medicinal product may be necessary.

Lamotrigine: Combined hormonal contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine when coadministered likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
EVRA is not indicated during pregnancy.

Epidemiological studies indicate no increased risk of birth defects in children born to women who used combined oral contraceptives prior to pregnancy. The majority of recent studies also do not indicate a teratogenic effect when combined oral contraceptives are used inadvertently during early pregnancy.

Limited data on the outcomes of exposed pregnancies in women using EVRA do not allow for conclusions about its safety during pregnancy.

Animal studies have shown undesirable effects during pregnancy and lactation (see section 5.3). Based on these animal data, undesirable effects due to hormonal action of the active compounds cannot be excluded. However, general experience with combined oral contraceptives during pregnancy did not provide evidence for an actual undesirable effect in humans.

If pregnancy occurs during use of EVRA, EVRA should be stopped immediately.

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

Breast-feeding
Breast-feeding may be influenced by combined hormonal contraceptives as they may reduce the quantity and change the composition of breast milk. Therefore, the use of EVRA is not to be recommended until the breast-feeding mother has completely weaned her child.

Fertility
Women may experience a delay in conception following discontinuation of EVRA.

4.7 Effects on ability to drive and use machines

EVRA has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in clinical trials were headache, nausea, and breast tenderness, occurring in approximately 21.0%, 16.6%, and 15.9% of patients, respectively. Adverse reactions that may occur at the beginning of treatment but usually diminish after the first three cycles include spotting, breast tenderness and nausea.

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.

Tabulated list of adverse reactions

Safety was evaluated in 3,322 sexually active women who participated in three Phase III clinical trials, which were designed to evaluate contraceptive efficacy. These subjects received six or 13 cycles of contraception (EVRA or oral contraceptive comparator), took at least one dose of study medicinal product and provided safety data. Table 1 below reflects the adverse reactions reported in clinical trials and from post-marketing experience. Frequency MedDRA convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 1: Frequency of adverse reactions

System Organ Class Frequency	**Adverse reaction**
Infections and infestations	
Common	(Vulvo) vaginal fungal infection Vaginal candidiasis
rare	Rash pustular* Application site pustules
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
rare	Hepatic neoplasm*† Breast cancer*† Cervix carcinoma*† Hepatic adenoma*† Uterine leiomyoma Fibroadenoma of breast
Immune system disorders	
uncommon	Hypersensitivity
rare	Anaphylactic reaction*
Metabolism and nutrition disorders	
Uncommon	Hypercholesterolaemia Fluid retention Increased appetite
rare	Hyperglycaemia* Insulin resistance*
Psychiatric disorders	
Common	Mood, affect and anxiety disorders
Uncommon	Insomnia Libido decreased
rare	Anger* Frustration* Libido increased
Nervous system disorders	
very common	Headache
common	Migraine Dizziness
Rare	Cerebrovascular accident**† Cerebral haemorrhage*† Abnormal taste*
Eye disorders	
rare	Contact lens intolerance*
Cardiac disorders	
rare	Arterial thromboembolism (Acute) myocardial infarction*†
Vascular disorders	
Uncommon	Hypertension

rare	Hypertensive crisis* Arterial thrombosis**† Venous thrombosis**† Thrombosis*† Venous thromboembolism
Respiratory, thoracic and mediastinal disorders	
rare	Pulmonary (artery) thrombosis*† Pulmonary embolism†
Gastrointestinal disorders	
very common common rare	Nausea Abdominal pain Vomiting Diarrhoea Abdominal distension Colitis*
Hepatobiliary disorders	
rare	Cholecystitis Cholelithiasis† Hepatic lesion* Jaundice cholestatic*† Cholestasis*†
Skin and subcutaneous tissue disorders	
Common Uncommon rare	Acne Rash Pruritus Skin reaction Skin irritation Alopecia Dermatitis allergic Eczema Photosensitivity reaction Dermatitis contact Urticaria Erythema Angioedema* Erythema (multiforme, nodosum)* Chloasma† Exfoliative rash* Pruritus generalised Rash (erythematous, pruritic) Seborrhoeic dermatitis*
Musculoskeletal and connective tissue disorders	
common	Muscle spasms
Reproductive system and breast disorders	
very common common	Breast tenderness Dysmenorrhoea Vaginal bleeding and menstrual disorders**† Uterine spasm Breast disorders Vaginal discharge

uncommon	Galactorrhoea Premenstrual syndrome Vulvovaginal dryness
rare	Cervical dysplasia* Suppressed lactation* Genital discharge
General disorders and administration site conditions	
Common	Malaise Fatigue Application site reactions (erythema, irritation, pruritus, rash)
uncommon	Generalised oedema Oedema peripheral Application site reactions**
rare	Face oedema* Pitting oedema* Swelling Application site reactions* (e.g., abscess, erosion) Localised oedema*
Investigations	
Common	Weight increased
Uncommon	Blood pressure increased Lipid disorders**
Rare	Blood glucose decreased*† Blood glucose abnormal*†

* Post-marketing reports.
** Includes adverse reactions reported in clinical trials and post-marketing reports.
† See section 4.4.

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

Serious ill effects have not been reported following accidental ingestion of large doses of oral contraceptives. Overdose may cause nausea or vomiting. Vaginal bleeding may occur in some females. In cases of suspected overdose, all transdermal contraceptive systems should be removed and symptomatic treatment given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, progestogens and estrogens, fixed combination; ATC-code: G03AA13.

Mechanism of action

EVRA acts through the mechanism of gonadotropin suppression by the estrogenic and progestational actions of ethinyl estradiol and norelgestromin. The primary mechanism of action is inhibition of the ovulation, but the alterations of the cervical mucus, and to the endometrium may also contribute to the efficacy of the product.

Clinical efficacy and safety

Pearl Indices (see table):

Study Group	CONT-002 EVRA	CONT-003 EVRA	CONT-003 COC*	CONT-004 EVRA	CONT-004 COC**	All EVRA Subjects
# of cycles	10,743	5,831	4,592	5,095	4,005	21,669
Overall Pearl Index (95% CI)	0.73 (0.15; 1.31)	0.89 (0.02; 1.76)	0.57 (0.0; 1.35)	1.28 (0.16; 2.39)	2.27 (0.59; 3.96)	0.90 (0.44; 1.35)
Method Failure Pearl Index (95% CI)	0.61 (0.0; 1.14)	0.67 (0.0; 1.42)	0.28 (0.0; 0.84)	1.02 (0.02; 2.02)	1.30 (0.03; 2.57)	0.72 (0.31; 1.13)

* DSG 150 µg + 20 µg EE

**50 µg LNG + 30 µg for days 1 – 6, 75 µg LNG + 40 µg EE for days 7 – 11, 125 µg LNG + 30 µg EE for 12 – 21 days

Exploratory analyses were performed to determine whether in the Phase III studies (n=3,319) the population characteristics of age, race and weight were associated with pregnancy. The analyses indicated no association of age and race with pregnancy. With respect to weight, 5 of the15 pregnancies reported with EVRA were among women with baseline body weight equal or greater than 90 kg, which constituted < 3% of the study population. Below 90 kg there was no association between body weight and pregnancy. Although only 10-20% of the variability in pharmacokinetic data can be explained by weight (see section 5.2), the greater proportions of pregnancies among women at or above 90 kg was statistically significant and indicates the EVRA is less effective in these women.

With the use of higher dosed COCs (50 microgram ethinyl estradiol) the risk of endometrial and ovarian cancer is reduced. Whether this is also applies to the lower dosed combined hormonal contraceptives remains to be confirmed.

5.2 Pharmacokinetic properties

Absorption

Following application of EVRA, norelgestromin and ethinyl estradiol levels in serum reach a plateau by approximately 48 hours. Steady state concentrations of norelgestromin and EE during one week of transdermal patch wear are approximately 0.8 ng/ml and 50 pg/ml, respectively. In multiple-dose studies, serum concentrations and AUC for norelgestromin and EE were found to increase only slightly over time when compared to week 1 cycle 1.

The absorption of norelgestromin and ethinyl estradiol following application of EVRA was studied under conditions encountered in a health club (sauna, whirlpool, treadmill and other aerobic exercise) and in a cold water bath. The results indicated that for norelgestromin there were no significant treatment effects on C_{ss} or AUC when compared to normal wear. For EE, slight increases were observed due to treadmill and other aerobic exercise; however, the C_{ss} values following these treatments were within the reference range. There was no significant effect of cool water on these parameters.

Results from an EVRA study of extended wear of single contraceptive transdermal patch for 7 days and 10 days indicated that target C_{ss} of norelgestromin and ethinyl estradiol were maintained during a 3-day period of extended wear of EVRA (10 days). These findings suggest that clinical efficacy would be maintained even if a scheduled change is missed for as long as 2 full days.

Distribution

Norelgestromin and norgestrel (a serum metabolite of norelgestromin) are highly bound (> 97%) to serum proteins. Norelgestromin is bound to albumin and not to SHBG, while norgestrel is bound primarily to SHBG, which limits its biological activity. Ethinyl estradiol is extensively bound to serum albumin.

Biotransformation

Hepatic metabolism of norelgestromin occurs and metabolites include norgestrel, which is largely bound to SHBG, and various hydroxylated and conjugated metabolites. Ethinyl estradiol is also metabolised to various hydroxylated products and their glucuronide and sulfate conjugates.

Elimination

Following removal of a transdermal patch, the mean elimination half-lives of norelgestromin and ethinyl estradiol were approximately 28 hours and 17 hours, respectively. The metabolites of norelgestromin and ethinyl estradiol are eliminated by renal and fecal pathways.

Transdermal versus Oral Contraceptives

The pharmacokinetic profiles of transdermal and oral combined hormonal contraceptives are different and caution should be exercised when making a direct comparison of these PK parameters.

In a study comparing EVRA to an oral contraceptive containing norgestimate (parent drug of norelgestromin) 250 mcg /ethinyl estradiol 35 mcg, C_{max} values were 2-fold higher for NGMN and EE in subjects administered the oral contraceptive compared to EVRA, while overall exposure (AUC and C_{ss}) was comparable in subjects treated with EVRA. Inter-subject variability (%CV) for the PK parameters following delivery from EVRA was higher relative to the variability determined from the oral contraceptive.

Effects of age, body weight, and body surface area

The effects of age, body weight, and body surface area on the pharmacokinetics of norelgestromin and ethinyl estradiol were evaluated in 230 healthy women from nine pharmacokinetic studies of single 7-day applications of EVRA. For both norelgestromin and EE, increasing age, body weight and body surface area each were associated with slight decreases in C_{ss} and AUC values. However, only a small fraction (10 – 20%) of the overall variability in the pharmacokinetics of the norelgestromin and EE following application of EVRA may be associated with any or all of the above demographic parameters.

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 and carcinogenic potential. With respect to the reproductive toxicity norelgestromin showed foetal toxicity in rabbits, but the safety margin for this effect was sufficiently high. Data on reproductive toxicity of the combination of norelgestromin with ethinyl estradiol are not available. Data for combination of norgestimate (precursor of norelgestromin) with ethinyl estradiol indicate for female animals a decrease in fertility and implantation efficiency (rat), an increase in foetal resorption (rat, rabbit) and, with high dosages, a decrease in viability and fertility of female offspring (rat). The relevance of these

data for human exposure is unknown as these effects have been seen as related to well-known pharmacodynamic or species-specific actions.

Studies conducted to examine the dermal effect of EVRA indicate this system has no potential to produce sensitisation and results in only mild irritation when applied to rabbits skin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layerlow-density pigmented polyethylene outer layer
polyester inner layer

Middle layer
polyisobutylene/polybutene adhesive
crospovidone,
non-woven polyester fabric,
lauryl lactate.
Release Liner

Third layer
polyethylene terephthalate (PET) film
polydimethylsiloxane coating.

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Do not store above 25 °C.

Store in the original package in order to protect from light and moisture.
Do not store in the refrigerator or freezer.

6.4 Nature and contents of container

Primary packaging material
A sachet is composed of four layers: a low-density polyethylene film (innermost layer), an aluminium foil, a low-density polyethylene film, and an outer layer of bleached paper.

Secondary packaging material
Sachets are packaged in a cardboard carton.
Every carton has 3, 9 EVRA transdermal patches in individual foil-lined sachets.
Sachets are wrapped per three in a transparent perforated plastic film and packed in a cardboard carton.

6.5 Special precautions for disposal and other handling

The patch should be applied immediately upon removal from the protective sachet.

To prevent interference with the adhesive properties of EVRA, no creams, lotions or powders should be applied to the skin area where the EVRA transdermal patch is to be applied.

After use the transdermal patch still contains substantial quantities of active ingredients. Remaining hormonal active ingredients of the transdermal patch may have harmful effects if reaching the aquatic environment. Therefore, the used transdermal patch should be discarded carefully. The disposal label from the outside of the sachet should be peeled open. The used transdermal patch should be placed within the open disposal label so that the sticky surface covers the shaded area on the sachet. The disposal label should then be closed sealing the used transdermal patch within. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Used transdermal patches should not be flushed down the toilet nor placed in liquid waste disposal systems.

Expiry date/shelf life: The expiry date of the product is indicated on the packaging materials

7. Importer and Registration Holder:

J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel

8. Registration Number
130-21-30818-00

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