ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EVRA 203 micrograms/24 hours + 33.9 micrograms/24 hours 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 and heat-stamped “EVRA”.

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 6.6.

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.

If subsequent EVRA transdermal patch change days are delayed

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.

Change day adjustment
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

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.**

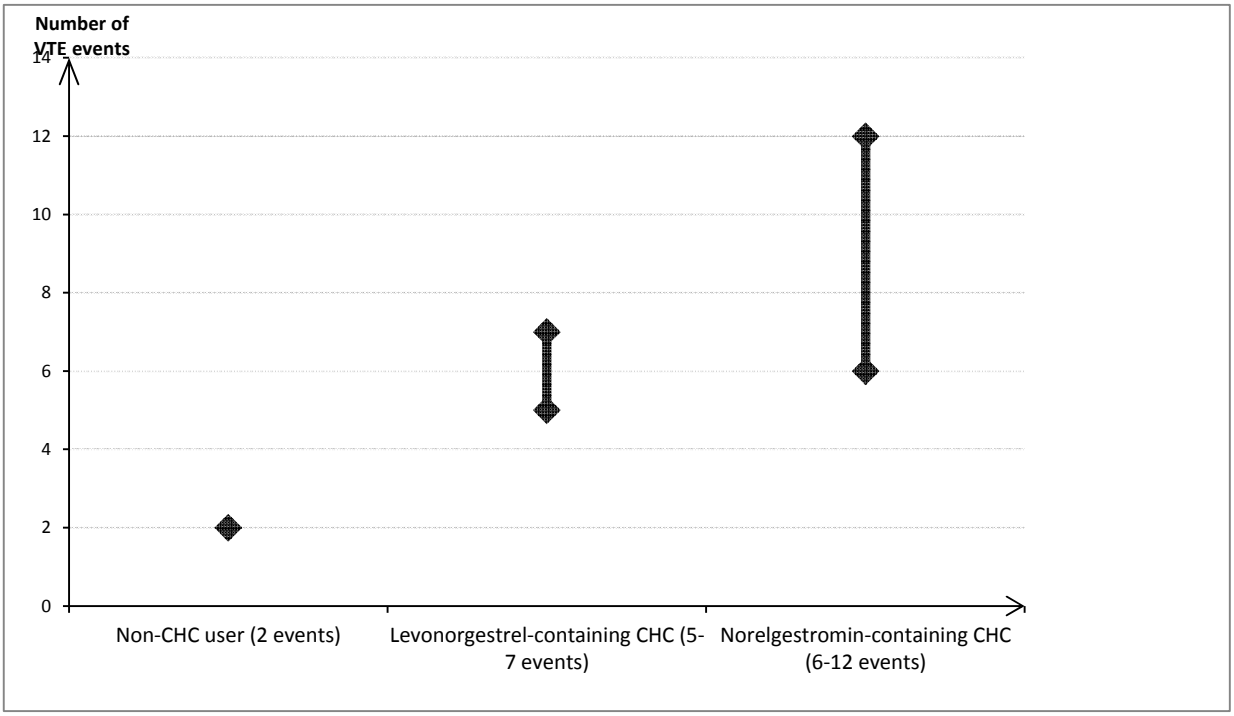
In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

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.

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.

[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

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.

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.

Influence of other medicinal products on EVRA
Interactions between oral contraceptives and other medicinal products may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

Hepatic metabolism
Interactions can occur with medicinal products that induce hepatic enzymes which can result in increased clearance of sex hormones (e.g. phenobarbital, primidone, rifampicin, rifabutin, bosentan, (fos)aprepitant), some anti-epileptics (e.g. carbamazepine, eslicarbazepine acetate, felbamate, oxcarbazepine, phenytoin, rufinamide, topiramate) and some HIV-medicinal products (e.g. nelfinavir, ritonavir, nevirapine, efavirenz) and possibly also griseofulvin and products containing the herbal remedy St. John's Wort (*Hypericum perforatum*).

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.

Herbal preparations containing St. John's Wort (*Hypericum perforatum*) should not be used while taking EVRA.

Interference with enterohepatic circulation
Contraceptive failures have also been reported with antibiotics, such as penicillins and tetracyclines. The mechanism of this effect has not been elucidated. In a pharmacokinetic interaction study, oral administration of tetracycline hydrochloride, 500 mg four times daily for 3 days prior to and 7 days during wear of EVRA, did not significantly affect the pharmacokinetics of norelgestromin or EE.

Management
Women on short-term treatment with any of the above-mentioned classes of medicinal products or individual active substances that induce hepatic enzymes (except rifampicin) should temporarily use a barrier method in addition to EVRA, i.e. during the time of concomitant medicinal product administration and for 7 days after their discontinuation. For women on rifampicin a barrier method should be used in addition to EVRA during the time of rifampicin administration and for 28 days after its discontinuation.

In women on long-term treatment with any of the above-mentioned classes of medicinal products, another reliable, non-hormonal, method of contraception is recommended.

Women on treatment with antibiotics (besides rifampicin, see above) should use the barrier method until 7 days after discontinuation.

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

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.

Influence 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
Metabolism and nutrition disorders	
uncommon rare	Hypercholesterolaemia Fluid retention Increased appetite Hyperglycaemia* Insulin resistance*
Psychiatric disorders	
common uncommon rare	Mood, affect and anxiety disorders Insomnia Libido decreased Anger* Frustration* Libido increased
Nervous system disorders	
very common common rare	Headache Migraine Dizziness Cerebrovascular accident**† Cerebral haemorrhage*† Abnormal taste*
Eye disorders	
rare	Contact lens intolerance*
Cardiac disorders	
rare	Arterial thromboembolism (Acute) myocardial infarction*†
Vascular disorders	
uncommon rare	Hypertension Hypertensive crisis* Arterial thrombosis**† Venous thrombosis**† Thrombosis*† Venous thromboembolism
Respiratory, thoracic and mediastinal disorders	
rare	Pulmonary (artery) thrombosis*† Pulmonary embolism†
Gastrointestinal disorders	
very common	Nausea

common	Abdominal pain Vomiting Diarrhoea Abdominal distension
rare	Colitis*
Hepatobiliary disorders	
rare	Cholecystitis Cholelithiasis† Hepatic lesion* Jaundice cholestatic*† Cholestasis*†
Skin and subcutaneous tissue disorders	
common	Acne Rash Pruritus Skin reaction Skin irritation
uncommon	Alopecia Dermatitis allergic Eczema Photosensitivity reaction Dermatitis contact Urticaria Erythema
rare	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	Breast tenderness
common	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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 the 15 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 faecal 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 μg/ethinyl estradiol 35 μg, 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 layer
low-density pigmented polyethylene outer layer
polyester inner layer.

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

Third layer
polyethylene terephthalate (PET) film
polydimethylsiloxane coating.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.
Do not refrigerate or freeze.

6.5 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 or 18 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.
Not all pack sizes may be marketed.

6.6 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.

7. MARKETING AUTHORISATION HOLDER

JANSSEN-CILAG INTERNATIONAL NV
Turnhoutseweg, 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/223/001
EU/1/02/223/002
EU/1/02/223/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 22 August 2002.
Date of latest renewal: 22 August 2012.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse, Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

EVRA 203 micrograms/24 hours + 33.9 micrograms/24 hours transdermal patch
norelgestromin/ethinyl estradiol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 patch of 20 cm^2 contains: 6 mg norelgestromin and 600 micrograms ethinyl estradiol

1 patch releases: 203 micrograms norelgestromin and 33.9 micrograms ethinyl estradiol per 24 hours

3. LIST OF EXCIPIENTS

Backing layer: low-density pigmented polyethylene outer layer, polyester inner layer.

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

Third layer: polyethylene terephthalate (PET) film, polydimethylsiloxane coating.

4. PHARMACEUTICAL FORM AND CONTENTS

3 transdermal patches
9 transdermal patches
18 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Do not flush used or unused patches down the toilet. See enclosed leaflet for disposal instructions.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg, 30
B-2340 Beerse, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/223/001: 3 transdermal patches
EU/1/02/223/002: 9 transdermal patches
EU/1/02/223/003: 18 transdermal patches

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

evra

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

EVRA 203 micrograms/24 hours + 33.9 micrograms/24 hours transdermal patch

norelgestromin/ethinyl estradiol

2. METHOD OF ADMINISTRATION

Transdermal use
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contains 1 transdermal patch

6. OTHER

Reminder stickers

Use these stickers on your calendar
to help you remember when to
change your patch

			Current Cycle	*Next Cycle*
First Patch (Week 1)	**Second Patch (Week 2)**	**Third Patch (Week 3)**	**Remove Patch Get New Patch**	**First patch**

Patch disposal label

PATCH DISPOSAL LABEL

To dispose of used patch:
1. place used patch so that the sticky side covers the shaded area
2. remove backing paper
3. close adhesive label and seal
4. discard with solid waste

B. PACKAGE LEAFLET

Package leaflet: Information for the user

EVRA 203 micrograms/24 hours + 33.9 micrograms/24 hours transdermal patch
norelgestromin/ethinyl estradiol

Important things to know about combined hormonal contraceptives (CHCs):
- They are one of the most reliable reversible methods of contraception if used correctly.
- They slightly increase the risk of having a blood clot in the veins and arteries, especially in the first year or when restarting a combined hormonal contraceptive following a break of 4 or more weeks.
- Please be alert and see your doctor if you get symptoms of a blood clot (see section 2 “Blood clots”).

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EVRA is and what it is used for

EVRA contains two types of sex hormones, a progestogen called norelgestromin and an oestrogen called ethinyl estradiol.

Because it contains two hormones, EVRA is called a ‘combined hormonal contraceptive’.

It is used to prevent pregnancy.

2. What you need to know before you use EVRA

General notes
Before you start using EVRA you should read the information on blood clots in section 2. It is particularly important to read the symptoms of a blood clot - see section 2 “Blood clots”.

When you should not use EVRA
You should not use EVRA if you have any of the conditions listed below. If you do have any of the conditions listed below, you must tell your doctor. Your doctor will discuss with you what other form of birth control would be more appropriate.
- if you have (or have ever had) a blood clot in a blood vessel of your legs (deep vein thrombosis, DVT), your lungs (pulmonary embolus, PE) or other organs;
- if you know you have a disorder affecting your blood clotting - for instance, protein C deficiency, protein S deficiency, antithrombin-III deficiency, Factor V Leiden or antiphospholipid antibodies;
- if you need an operation or if you are off your feet for a long time (see section ‘Blood clots)’;
- if you have ever had a heart attack or a stroke;

- if you have (or have ever had) angina pectoris (a condition that causes severe chest pain and may be a first sign of a heart attack) or transient ischaemic attack (TIA – temporary stroke symptoms);
- if you have a disease that may increase your risk of a clot in the arteries:
  - severe diabetes with blood vessel damage
  - very high blood pressure
  - a very high level of fat in the blood (cholesterol or triglycerides)
  - a condition known as hyperhomocysteinaemia
- if you have (or have ever had) a type of migraine called 'migraine with aura';
- if you are allergic to norelgestromin, ethinyl estradiol or any of the other ingredients of this medicine (listed in section 6);
- if you have ever been told you might have breast cancer or cancer of the womb, cervix or vagina;
- if you have ever had liver tumours or a liver disease because of which your liver does not function properly;
- if you have unexplained vaginal bleeding.

Do not use this medicine if any of the above applies to you. If you are not sure, talk to your doctor, pharmacist or nurse before using this medicine.

When to take special care with EVRA

When should you contact your doctor?

Seek urgent medical attention
- if you notice possible signs of a blood clot that may mean you are suffering from a blood clot in the leg (i.e. deep vein thrombosis), a blood clot in the lung (i.e. pulmonary embolism), a heart attack or a stroke (see 'Blood clot [thrombosis] section below).

For a description of the symptoms of these serious side effects please go to "How to recognise a blood clot".

Warnings and precautions

Before using this medicine, you will need to see your doctor for a medical check-up.

Tell your doctor if any of the following conditions apply to you.

If the condition develops, or gets worse while you are using EVRA, you must tell your doctor.
- if you have Crohn's disease or ulcerative colitis (chronic inflammatory bowel disease);
- if you have SLE (systemic lupus erythematosus; a disease affecting your natural defence system);
- if you have haemolytic uraemic syndrome (HUS - a disorder of blood clotting causing failure of the kidneys);
- if you have sickle cell anaemia (an inherited disease of the red blood cells);
- if you have elevated levels of fat in the blood (hypertriglyceridaemia) or a positive family history for this condition. Hypertriglyceridaemia has been associated with an increased risk of developing pancreatitis (inflammation of the pancreas);
- if you need an operation, or you are off your feet for a long time (see in section 2 'Blood clots');
- if you have just given birth you are at an increased risk of blood clots. You should ask your doctor how soon after delivery you can start taking EVRA;
- if you have an inflammation in the veins under the skin (superficial thrombophlebitis);
- if you have varicose veins.

BLOOD CLOTS

Using a combined hormonal contraceptive such as EVRA increases your risk of developing a blood clot compared with not using one. In rare cases a blood clot can block blood vessels and cause serious problems.

Blood clots can develop

- in veins (referred to as a 'venous thrombosis', 'venous thromboembolism' or VTE)
- in the arteries (referred to as an 'arterial thrombosis', 'arterial thromboembolism' or ATE).

Recovery from blood clots is not always complete. Rarely, there may be serious lasting effects or, very rarely, they may be fatal.

It is important to remember that the overall risk of a harmful blood clot due to EVRA is small.

HOW TO RECOGNISE A BLOOD CLOT

Seek urgent medical attention if you notice any of the following signs or symptoms.

Are you experiencing any of these signs?	What are you possibly suffering from?
● swelling of one leg or along a vein in the leg or foot especially when accompanied by: - pain or tenderness in the leg which may be felt only when standing or walking; - increased warmth in the affected leg; - change in colour of the skin on the leg e.g. turning pale, red or blue.	Deep vein thrombosis
● sudden unexplained breathlessness or rapid breathing; ● sudden cough without an obvious cause, which may bring up blood; ● sharp chest pain which may increase with deep breathing; ● severe light headedness or dizziness; ● rapid or irregular heartbeat; ● severe pain in your stomach. If you are unsure, talk to a doctor as some of these symptoms such as coughing or being short of breath may be mistaken for a milder condition such as a respiratory tract infection (e.g. a 'common cold').	Pulmonary embolism
Symptoms most commonly occur in one eye: ● immediate loss of vision or; ● painless blurring of vision which can progress to loss of vision.	Retinal vein thrombosis (blood clot in the eye)
● chest pain, discomfort, pressure, heaviness; ● sensation of squeezing or fullness in the chest, arm or below the breastbone; ● fullness, indigestion or choking feeling; ● upper body discomfort radiating to the back, jaw, throat, arm and stomach; ● sweating, nausea, vomiting or dizziness; ● extreme weakness, anxiety, or shortness of breath; ● rapid or irregular heartbeats.	Heart attack

● sudden weakness or numbness of the face, arm or leg, especially on one side of the body; ● sudden confusion, trouble speaking or understanding; ● sudden trouble seeing in one or both eyes; ● sudden trouble walking, dizziness, loss of balance or coordination; ● sudden, severe or prolonged headache with no known cause; ● loss of consciousness or fainting with or without seizure. Sometimes the symptoms of stroke can be brief with an almost immediate and full recovery, but you should still seek urgent medical attention as you may be at risk of another stroke.	Stroke
● swelling and slight blue discolouration of an extremity; ● severe pain in your stomach (acute abdomen).	Blood clots blocking other blood vessels

BLOOD CLOTS IN A VEIN

What can happen if a blood clot forms in a vein?
- The use of combined hormonal contraceptives has been connected with an increase in the risk of blood clots in the vein (venous thrombosis). However, these side effects are rare. Most frequently, they occur in the first year of use of a combined hormonal contraceptive.
- If a blood clot forms in a vein in the leg or foot it can cause a deep vein thrombosis (DVT).
- If a blood clot travels from the leg and lodges in the lung it can cause a pulmonary embolism.
- Very rarely a clot may form in a vein in another organ such as the eye (retinal vein thrombosis).

When is the risk of developing a blood clot in a vein highest?
The risk of developing a blood clot in a vein is highest during the first year of taking a combined hormonal contraceptive for the first time. The risk may also be higher if you restart taking a combined hormonal contraceptive (the same product or a different product) after a break of 4 weeks or more.

After the first year, the risk gets smaller but is always slightly higher than if you were not using a combined hormonal contraceptive.

When you stop EVRA your risk of a blood clot returns to normal within a few weeks.

What is the risk of developing a blood clot?
The risk depends on your natural risk of VTE and the type of combined hormonal contraceptive you are taking.

The overall risk of a blood clot in the leg or lung (DVT or PE) with EVRA is small.

- Out of 10,000 women who are not using any combined hormonal contraceptive and are not pregnant, about 2 will develop a blood clot in a year.
- Out of 10,000 women who are using a combined hormonal contraceptive that contains levonorgestrel, norethisterone, or norgestimate about 5-7 will develop a blood clot in a year.
- Out of 10,000 women who are using a combined hormonal contraceptive that contains etonorgestrel or norelgestromin such as EVRA between about 6 and 12 women will develop a blood clot in a year.
- The risk of having a blood clot will vary according to your personal medical history (see "Factors that increase your risk of a blood clot" below).

	Risk of developing a blood clot in a year
Women who are **not using** a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000 women
Women using a combined hormonal contraceptive pill containing **levonorgestrel, norethisterone or norgestimate**	About 5-7 out of 10,000 women

Women using EVRA	About 6-12 out of 10,000 women

Factors that increase your risk of a blood clot in a vein
The risk of a blood clot with EVRA is small but some conditions will increase the risk. Your risk is higher:

- if you are very overweight (body mass index or BMI over 30 kg/m^2);
- if one of your immediate family has had a blood clot in the leg, lung or other organ at a young age (e.g. below the age of about 50). In this case you could have a hereditary blood clotting disorder;
- if you need to have an operation, or if you are off your feet for a long time because of an injury or illness, or you have your leg in a cast. The use of EVRA may need to be stopped several weeks before surgery or while you are less mobile. If you need to stop EVRA ask your doctor when you can start using it again;
- as you get older (particularly above about 35 years);
- if you gave birth less than a few weeks ago.

The risk of developing a blood clot increases the more conditions you have.

Air travel (> 4 hours) may temporarily increase your risk of a blood clot, particularly if you have some of the other factors listed.

It is important to tell your doctor if any of these conditions apply to you, even if you are unsure. Your doctor may decide that EVRA needs to be stopped.

If any of the above conditions change while you are using EVRA, for example a close family member experiences a thrombosis for no known reason; or you gain a lot of weight, tell your doctor.

BLOOD CLOTS IN AN ARTERY

What can happen if a blood clot forms in an artery?
Like a blood clot in a vein, a clot in an artery can cause serious problems. For example, it can cause a heart attack or a stroke.

Factors that increase your risk of a blood clot in an artery
It is important to note that the risk of a heart attack or stroke from using EVRA is very small but can increase:

- with increasing age (beyond about 35 years);
- **if you smoke**. When using a combined hormonal contraceptive like EVRA you are advised to stop smoking. If you are unable to stop smoking and are older than 35 your doctor may advise you to use a different type of contraceptive;
- if you are overweight;
- if you have high blood pressure;
- if a member of your immediate family has had a heart attack or stroke at a young age (less then about 50). In this case you could also have a higher risk of having a heart attack or stroke;
- if you, or someone in your immediate family, have a high level of fat in the blood (cholesterol or triglycerides);
- if you get migraines, especially migraines with aura;
- if you have a problem with your heart (valve disorder, disturbance of the rhythm called atrial fibrillation);
- if you have diabetes.

If you have more than one of these conditions or if any of them are particularly severe the risk of developing a blood clot may be increased even more.

If any of the above conditions change while you are using EVRA, for example you start smoking, a close family member experiences a thrombosis for no known reason; or you gain a lot of weight, tell your doctor.

Additionally, talk to your doctor, pharmacist or nurse before using EVRA if you have any of the following or they happen or get worse while using EVRA:

- You think you might be pregnant;
- You have headaches that get worse or happen more often;
- You weigh 90 kg (which is 14 stone 2 lb) or more;
- You have high blood pressure or your blood pressure gets higher;
- You have gallbladder disease including gallstones or inflammation of the gallbladder;
- You have a blood problem called porphyria;
- You have a problem of the nervous system involving sudden movements of the body called 'Sydenham's chorea';
- You had a skin rash with blisters during pregnancy (called 'herpes gestationis');
- You have a hearing loss;
- You have diabetes;
- You have depression;
- You have epilepsy or any other problem that can cause fits (convulsions);
- You have liver problems including yellowing of the skin and whites of the eye (jaundice);
- You have or have had 'pregnancy spots'. These are yellowish-brown patches or spots, especially on your face (called 'chloasma'). These spots may not go away completely, even after you stop using EVRA. Protect your skin from sunlight or ultraviolet radiation. This may help prevent you from getting these spots or help prevent them from getting worse.
- You have kidney problems.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using EVRA.

Sexually transmitted disease
This medicine will not protect you against HIV infection (AIDS) or any other sexually transmitted disease. These include chlamydia, genital herpes, genital warts, gonorrhoea, hepatitis B, syphilis. Always use condoms to protect yourself from these diseases.

Medical tests

- If you need a blood or urine test, tell your doctor or the laboratory staff that you are taking EVRA, because hormonal contraceptives can affect the results of some tests.

Children and adolescents
EVRA has not been studied in children and adolescents under 18 years of age. EVRA must not be used in children and adolescents who have not yet had their first menstrual period.

Other medicines and EVRA
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Certain medicines and herbal therapies may stop EVRA from working properly. If this happens you could get pregnant.

Tell your doctor if you are taking:

- some antiretroviral medicines used to treat HIV/AIDS (such as nelfinavir, ritonavir, nevirapine, efavirenz)
- medicines for infection (such as rifampicin, rifabutin and griseofulvin, penicillins and tetracycline)
- anti-seizure medicines (such as topiramate, phenobarbital, phenytoin, carbamazepine, primidone, oxcarbamazepine, felbamate, eslicarbazepine acetate and rufinamide)
- (fos)aprepitant (a medicine to treat nausea)
- bosentan (a medicine for high blood pressure in the blood vessels in the lungs)
- St. John's wort (an herbal therapy used for depression). St. John's wort should not be taken when you are using EVRA.

If you take any of these medicines, you may need to use another method of birth control (such as a condom, diaphragm or foam). The interfering effect of some of these medicines can last for up to 28 days after you have stopped taking them. Talk to your doctor or pharmacist about using another method of birth control if you use EVRA and any of the above medicines concomitantly.

EVRA may make some other medicines less effective, such as:
- medicines containing ciclosporin
- lamotrigine used for epilepsy [This can increase the risk of fits (seizures)].

Your doctor may need to adjust the dose of the other medicine. Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy and breast-feeding
- Do not use this medicine if you are pregnant or think you may be pregnant.
- Stop using this medicine right away if you become pregnant.
- Do not use this medicine if you are breast-feeding or planning to breast-feed.

If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
You can drive or use machines while using this medicine.

Risks of using combined hormonal contraceptives
The following information is based on information about combined birth control pills. As the EVRA transdermal patch contains similar hormones to those used in combined birth control pills, it is likely to have the same risks. All combined birth control pills have risks, which may lead to disability or death.

It has not been shown that a transdermal patch like EVRA is safer than a combined birth control pill taken by mouth.

Combined hormonal contraceptives and cancer

Cervical cancer
Cervical cancer has been found more often in women taking combined hormonal contraceptives. However, this may be due to other causes including sexually-transmitted disease.

Breast cancer
Breast cancer has been found more often in women who take combined hormonal contraceptives. However, it is possible that the combined hormonal contraceptive is not the cause of more women having breast cancer. It may be that women taking the combined hormonal contraceptive are examined more often. This might mean that there is a better chance of the breast cancer being noticed. The increased risk gradually goes down after stopping the combined hormonal contraceptive. After 10 years, the risk is the same as for people who have never used the combined hormonal contraceptive.

Liver cancer
In rare cases, liver tumours which are not cancer have been found in women taking combined hormonal contraceptives. Even more rarely, liver tumours which are cancer have been found. This can cause bleeding inside the body with very bad pain in the stomach area. **If this happens to you, talk to your doctor immediately.**

3. How to use EVRA

Always use this medicine exactly as your doctor or pharmacist has told you.

- If you do not, you may increase your risk of getting pregnant.
- Check with your doctor or pharmacist if you are not sure.
- Always keep non-hormonal contraceptives (such as condoms, foam or sponge) as a back-up in case you make a mistake when using the patch.

How many patches to use
- Weeks 1, 2 & 3: Put on one patch and leave it on for exactly seven days.
- Week 4: Do **not** put on a patch this week.

If you have not used a hormonal contraceptive during your previous cycle
- You may start this medicine on the first day of your next period.
- If one or more days have elapsed since the start of your period, talk to your doctor about temporarily using a non-hormonal contraceptive.

If you switch from the oral contraceptive pill to EVRA
If you are switching from an oral contraceptive pill to this medicine:
- Wait until you get your menstrual period.
- Put on your first patch during the first 24 hours of your period.

If the patch is applied after Day 1 of your period, you should:
- Use a non-hormonal contraceptive until Day 8 when you change your patch.

If you do not get your period within 5 days of taking the last contraceptive pill, check with your doctor before starting this medicine.

If you switch from the progestogen-only pill, an implant or an injectable to EVRA
- You may start this medicine any day after stopping the progestogen-only pill or on the day of removal of an implant or when the next injection would be due.
- The first day after stopping the progestogen-only pill, removing the implant or when your next injection would be due, put on a patch.
- Use a non-hormonal contraceptive until Day 8, when you change your patch.

After miscarriage or abortion *before* 20 weeks of pregnancy
- Talk to your doctor.
- You may start this medicine right away.

If one or more days have elapsed since your miscarriage or abortion when you start this medicine, talk to your doctor about temporarily using a non-hormonal contraceptive.

After miscarriage or abortion *after* 20 weeks of pregnancy
- Talk to your doctor.

You may start this medicine on Day 21 following the abortion or miscarriage, or on the first day of your next period, whichever comes first.

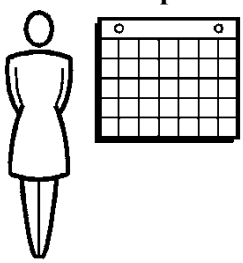
After delivery
- Talk to your doctor.
- If you've had a baby and are not breast-feeding, you should not start using this medicine sooner than 4 weeks after delivery.
- If you start more than 4 weeks after delivery, use another non-hormonal contraceptive in addition to this medicine for the first 7 days.

If you've had sex since delivery of your baby, wait for your first period or see your doctor to make sure you are not pregnant before starting this medicine.

If you are breast-feeding
- Talk to your doctor.
- Do not use this medicine if you are breast-feeding or planning to breast-feed (see also section 2 Pregnancy and breast-feeding).

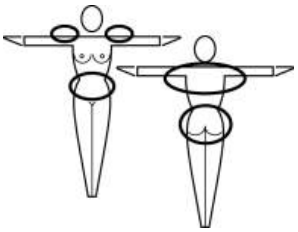
Important information to follow when using the patch
- Change EVRA on the same day of each week. This is because it is designed to work over 7 days.
- Never go without wearing a patch for more than 7 days in a row.
- Only wear one patch at a time.
- Do not cut or tamper with the patch in any way.
- Do not put the patch on skin that is red, irritated or cut.
- To work properly the patch must stick firmly to your skin.
- Press the patch down firmly until the edges stick well.
- Do not use creams, oils, lotions, powder or makeup on the skin where you are placing a patch or near a patch you are wearing. This may make the patch come loose.
- Do not put a new patch on the same area of skin as the old patch. If you do you are more likely to cause irritation.
- Check each day to make sure the patch has not fallen off.
- Keep using the patches even if you do not have sex very often.

How to use the patch:



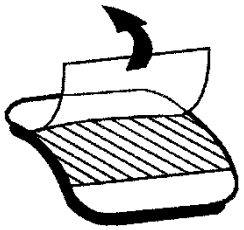
If this is the first time you are using EVRA, wait until the day you get your menstrual period.

- Apply your first patch during the first 24 hours of your period
- If the patch is put on after the first day of your period, use a non-hormonal contraceptive until Day 8, when you change your patch
- **The day you apply your first patch will be Day 1. Your "Patch Change Day" will be on this day of the week every week.**



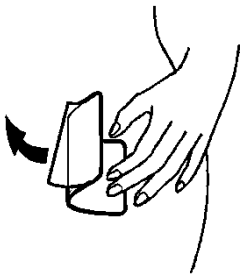
Choose a place on your body to put the patch.

- Always put your patch on clean, dry, hairless skin
- Put it on the buttock, abdomen, upper outer arm or upper back - places where it won't be rubbed by tight clothing
- **Never put the patch on your breasts**.



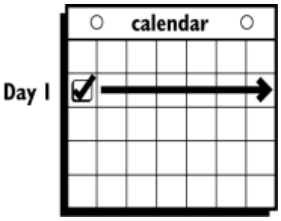
Using your fingers, open the foil sachet.

- Open it by tearing it along the edge (do not use scissors)
- Firmly grasp a corner of the patch and gently take it from the foil sachet
- There is a clear protective covering on the patch
- **Sometimes patches can stick to the inside of the sachet – be careful not to accidentally remove the clear covering as you remove the patch**
- Then peel away half of the clear protective covering (see picture). Try not to touch the sticky surface.



Put the patch on your skin.

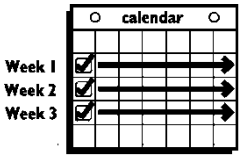
- Then take off the other half of the covering
- Press down firmly on the patch with the palm of your hand for 10 seconds
- Make sure that the edges stick well.



Wear the patch for 7 days (one week).

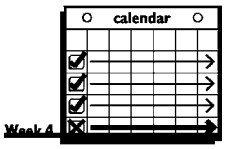
- On the first "Patch Change Day", Day 8, take off the used patch
- Put on a new patch immediately.

- On Day 15 (Week 3), take off the used patch
- Put on another new one.



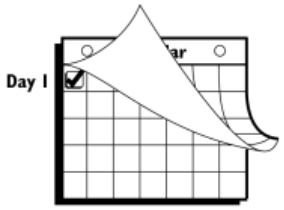
This makes a total of three weeks with the patches.

To help stop irritation, do not put the new patch on exactly the same area of your skin as your last patch.



Do not wear a patch on Week 4 (Day 22 through Day 28).

- **You should have your period during this time**
- During this week you are protected from getting pregnant only if you start your next patch on time.



For your next four week cycle.

- Put on a new patch on your normal "Patch Change Day", the day after Day 28
- **Do this no matter when your period begins or ends**.

If you want to change your "Patch Change Day" to a different day of the week talk to your doctor. You will need to complete the current cycle and remove the third patch on the correct day. During Week 4, you may pick a new Change Day and apply the first patch on that day. You should never go more than 7 days in a row without wearing a patch.

If you want to delay your period, apply a patch at the beginning of Week 4 (Day 22) instead of not wearing a patch on Week 4. You may experience light or breakthrough bleeding. Do not wear more than 6 patches (so not more than 6 weeks) in a row. When you have worn 6 patches in a row (so for 6 consecutive weeks), do not put on a patch in week 7. After 7 days of not wearing a patch, apply a new patch and restart the cycle using this as Day 1. Talk with your doctor before deciding to delay your period.

Everyday activities while using the patches

- Normal activities such as having a bath or shower, using a sauna and exercising should not affect how well the patch works.
- The patch is designed to stay in place during these types of activities.
- However, you should check that the patch has not fallen off after doing these activities.

If you need to place the patch on a new area on your body on a day other than your "Patch Change Day"
If the patch causes irritation or you become uncomfortable wearing it:
- You can take it off and replace it with a new patch in a different place on your body until your next "Patch Change Day"
- You may only use one patch at a time.

If you have trouble remembering to change your patch
- Talk to your doctor, pharmacist or nurse. He/she may be able to make patch changing easier for you. He/she may also talk about whether you need to use another method of contraception.

If your patch becomes loose, lifts at the edges or falls off

For less than one day (up to 24 hours):
- Try to put it on again or put on a new patch immediately.
- Back-up contraception is not needed.
- Your "Patch Change Day" should remain the same.
- Do not try to put a patch back on if:
  - it is no longer sticky
  - it has become stuck to itself or another surface
  - it has other material stuck to it
  - it is the second time it has become loose or has fallen off.
- Do not use tapes or wrapping to keep the patch in place.
- If you cannot get a patch back on, put on a new patch immediately.

For more than one day (24 hours or more) or if you are not sure for how long:
- Start a new four week cycle immediately by putting on a new patch.
- You now have a new Day 1 and a new "Patch Change Day".
- You must use non-hormonal contraception as back up for the first week of your new cycle.

You may get pregnant if you do not follow these instructions.

If you forget to change your patch

At the start of any patch cycle (Week 1 (Day 1)):
If you forget to put on your patch, you may be at particularly high risk of becoming pregnant.
- You must use non-hormonal contraception as back up for one week.
- Put on the first patch of your new cycle as soon as you remember.
- You now have a new "Patch Change Day" and new Day 1.

In the middle of your patch cycle (Week 2 or 3):
If you forget to change your patch for one or two days (up to 48 hours):
- You must put on a new patch as soon as you remember.
- Put on your next patch on your normal "Patch Change Day".

No back up contraception is needed.

For more than 2 days (48 hours or more)**:**
- If you forget to change your patch for more than 2 days, you may become pregnant.
- You must start a new four week cycle as soon as you remember by putting on a new patch.
- You now have a different "Patch Change Day" and a new Day 1.
- You must use back-up contraception for the first week of your new cycle.

At the end of your patch cycle (Week 4):
If you forget to take off your patch:
- Take it off as soon as you remember.

- Start your next cycle on your normal “Patch Change Day”, the day after Day 28.

No back-up contraception is needed.

If you have absent or irregular bleeding with EVRA
This medicine may cause unexpected vaginal bleeding or spotting during the weeks when you are wearing the patch.
- This usually stops after the first few cycles.
- Mistakes in using your patches can also cause spotting and light bleeding.
- Continue using this medicine and if the bleeding lasts more than the first three cycles, talk to your doctor or pharmacist.

If you do not get your period during the EVRA patch-free week (Week 4), you should still use a new patch on your usual “Patch Change Day”.
- If you have been using this medicine correctly and you do not have a period, this does not necessarily mean that you are pregnant.
- However, if you miss two periods in a row, talk to your doctor or pharmacist as you may be pregnant.

If you use more EVRA than you should (more than one EVRA patch at any one time)
Take the patches off and talk to a doctor immediately.

Using too many patches may cause you to have the following:
- Feeling sick (nausea) and being sick (vomiting)
- Bleeding from the vagina.

If you stop using EVRA
You may get irregular, little or no menstruation. This usually happens in the first 3 months and especially if your periods were not regular before you started using this medicine.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you get any side effect, particularly if severe and persistent, or have any change to your health that you think may be due to EVRA, please talk to your doctor.

An increased risk of blood clots in your veins [venous thromboembolism (VTE)] or blood clots in your arteries [arterial thromboembolism (ATE)] is present for all women taking combined hormonal contraceptives. For more detailed information on the different risks from taking combined hormonal contraceptives please see section 2 “What you need to know before you use EVRA”.

Very common side effects (may affect more than 1 in 10 women):
- Headache
- Nausea
- Breast tenderness.

Common side effects (may affect up to 1 in 10 women):
- Vaginal yeast infection, sometimes called thrush
- Mood problems such as depression, change in mood or mood swings, anxiety, crying
- Dizziness
- Migraine
- Stomach ache or bloating
- Vomiting or diarrhoea
- Acne, skin rash, skin itching or skin irritation

- Muscle spasms
- Breast problems such as pain, enlargement or lumps in the breast
- Changes in menstrual bleeding pattern, uterine cramps, painful periods, vaginal discharge
- Problems where the patch has been on the skin such as redness, irritation, itching or rash
- Feeling tired or generally unwell
- Weight gain.

Uncommon side effects (may affect up to 1 in 100 women):
- Allergic reaction, hives
- Swelling due to water retention in the body
- High levels of fats in the blood (such as cholesterol or triglycerides)
- Problems sleeping (insomnia)
- Less interest in sex
- Eczema, redness of the skin
- Abnormal breast milk production
- Premenstrual syndrome
- Vaginal dryness
- Other problems where the patch has been on the skin
- Swelling
- High blood pressure or rise in blood pressure
- Increased appetite
- Hair loss
- Sensitivity to sunlight.

Rare side effects (may affect up to 1 in 1,000 women):
- Harmful blood clots in a vein or artery for example:
  - in a leg or foot (i.e. DVT)
  - in a lung (i.e. PE)
  - heart attack
  - stroke
  - mini-stroke or temporary stroke-like symptoms, known as a transient ischaemic attack (TIA)
  - blood clots in the liver, stomach/intestine, kidneys or eye.

  The chance of having a blood clot may be higher if you have any other conditions that increase this risk (See section 2 for more information on the conditions that increase risk for blood clots and the symptoms of a blood clot).
- Breast, cervical or liver cancer
- Problems where the patch has been on the skin such as skin rash with blisters or ulcers
- Non-cancerous (benign) tumours in your breast or liver
- Fibroids in the womb (uterus)
- Anger or feeling frustrated
- Increased interest in sex
- Abnormal taste
- Problems when wearing contact lenses
- Sudden sharp increase in blood pressure (hypertensive crisis)
- Inflammation of the gall bladder or colon
- Abnormal cells in your cervix
- Brown spots or patches on the face
- Gallstones or blockage of the bile duct
- Yellowing of the skin and whites of the eyes
- Abnormal blood sugar or insulin levels
- Swelling of face, mouth, throat, or tongue
- Skin rash with tender red nodules on the shins and legs
- Itchy skin
- Scaly, flaky, itchy and red skin
- Suppressed lactation
- Vaginal discharge

- Fluid retention in legs
- Fluid retention
- Swelling in the arms, hands, legs or feet.

If you have an upset stomach
- The amount of hormones you get from EVRA should not be affected by being sick (vomiting) or diarrhoea.
- You do not need to use extra contraception if you have an upset stomach.

You may have spotting or light bleeding or breast tenderness or may feel sick during the first 3 cycles. The problem will usually go away but if it doesn't, check with your doctor or pharmacist.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store EVRA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the label after "EXP". The expiry date refers to the last day of that month.

Store in the original container to protect from light and moisture.

Do not refrigerate or freeze.

Used patches still contain some active hormones. To protect the environment, the patches should be disposed of with care. To discard the used patch, you should:
- Peel back the disposal label on the outside of the sachet.
- Place the used patch within the open disposal label so that the sticky surface covers the shaded area.
- Close the label sealing the used patch within and discard, keeping out of reach of children.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What EVRA contains
The active substances are norelgestromin and ethinyl estradiol. Each 20 cm^2 transdermal patch contains 6 mg norelgestromin and 600 micrograms ethinyl estradiol. The active substances are released over 7 days with an average of 203 micrograms norelgestromin and 34 micrograms ethinyl estradiol being released each 24 hours.

The other ingredients are: backing layer: low-density pigmented polyethylene outer layer, polyester inner layer; middle layer: polyisobutylene/polybutene adhesive, crospovidone, non-woven polyester fabric, lauryl lactate; third layer: polyethylene terephthalate (PET) film, polydimethylsiloxane coating.

What EVRA looks like and contents of the pack
EVRA is a thin, beige, plastic transdermal patch stamped "EVRA". The sticky adhesive side is stuck to the skin after removal of the clear, plastic, protective covering.

EVRA is available in the following pack sizes: Cartons containing 3, 9 or 18 patches in individual foil-lined sachets, wrapped per three in a transparent perforated plastic film.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Janssen-Cilag International NV Turnhoutseweg, 30, B-2340 Beerse, Belgium.

Manufacturer: Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse, Belgium.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.