**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

EVRA transdermal patch

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each transdermal patch releases 150 micrograms of NGMN and 20 micrograms of EE per 24 h.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Transdermal patch.

EVRA is a thin, matrix-type transdermal patch consisting of three layers.

The outside of the backing layer is beige and heat-stamped “EVRA 150/20”.

## 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.

### 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 patch is to be worn at a time.

Each used 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. Patch changes may occur at any time on the scheduled Change Day. The fourth week is patch-free starting on Day 22.

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

Under no circumstances should there be more than a 7-day patch-free interval between dosing cycles. If there are more than 7 patch-free days, the user may not be protected against pregnancy. A non-hormonal contraceptive must then be used concurrently for 7 days. As with combined oral contraceptives, the risk of ovulation increases with each day beyond the recommended contraceptive-free period. If intercourse has occurred during such an extended patch-free interval, the possibility of fertilisation should be considered.

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

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

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

Used 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 patch is applied and worn for one full week (7 days). The day the first patch is applied (Day 1/Start Day) determines the subsequent Change Days. The 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 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 minipill (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.

What to do if the patch comes off or partly detaches

If the EVRA 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 patch immediately. No additional contraceptive is needed. The next EVRA 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 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 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 patch should not be reapplied if it is no longer sticky; a new patch should be applied immediately. Supplemental adhesives or bandages should not be used to hold the EVRA patch in place.

If subsequent EVRA patch change days are delayed

*At the start of any patch cycle (Week One/Day 1):*

The user may not be protected from pregnancy. The user should apply the first patch of the new cycle as soon as remembered. There is now a new 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 patch-free interval, the possibility of fertilisation 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 patch immediately. The next EVRA patch should be applied on the usual "Change Day". If during the 7 days preceding the first skipped day of patch application, the 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 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 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 patch at the beginning of Week 4 (Day 22) thus not observing the patch free interval. Breakthrough bleeding or spotting may occur. After 6 consecutive weeks of patch wear, there should be a 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 patch on the correct day. During the patch-free week a new Change Day may be selected by applying the first EVRA patch of the next cycle on the first occurrence of the desired day. In no case should there be more than 7 consecutive patch-free days. The shorter the 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 patch use results in uncomfortable irritation, a new patch may be applied to a new location until the next Change Day. Only one patch should be worn at a time.

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 intended for use as hormonal replacement therapy.

*Children and adolescents:* EVRA is not recommended for use in children and adolescents under age 18 due to insufficient data on safety and efficacy.

## 4.3 Contraindications

EVRA should not be used in the presence of one of the following disorders. If one of these disorders occurs during the use of EVRA, EVRA must be discontinued immediately.

- Hypersensitivity to the active substances or to any of the excipients
- Presence or history of venous thrombosis, with or without the involvement of pulmonary embolism
- Presence or history of arterial thrombosis (e.g., cerebrovascular accident, myocardial infarction, retinal thrombosis) or prodrome of a thrombosis (e.g., angina pectoris or transient ischaemic attack)
- Migraine with focal aura
- The presence of serious or multiple risk factor(s) for the occurrence of arterial thrombosis:
- Severe hypertension (Persistent blood pressure values of ≥160 mm Hg systolic or ≥100 mm Hg diastolic)
- Diabetes Mellitus with vascular involvement
- Hereditary dyslipoproteinemia
- Possible hereditary predisposition for venous or arterial thrombosis, such as activated protein C (APC-) resistance, antithrombin-III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant)

- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-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

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).

If any of the conditions/risk factors mentioned below is present, the benefits of the use of EVRA should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using EVRA. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should be emphatically told to contact her physician who will decide on whether its use should be discontinued.

Thromboembolic and other vascular disorders

The use of any combined hormonal contraceptive, including EVRA, carries an increased risk of venous thromboembolism (deep vein thrombosis, pulmonary embolism) compared to no use. Epidemiological studies have shown that the incidence of venous thromboembolism (VTE) in women with no other risk factors for VTE who use low dose oestrogen (<50 micrograms ethinyl estradiol) combined contraceptives ranges from about 20 to 40 cases per 100,000 women-years, but this risk estimate varies according to the type of progestagen. This compares with 5 to 10 cases per 100,000 women-years for non-users and 60 cases per 100,000 pregnancies. VTE is fatal in 1%-2% of cases.

Data from a retrospective cohort study in women aged 15 to 44 years have suggested that the incidence of VTE in women who used EVRA is increased in comparison with users of a levonorgestrel-containing OC (so-called “second generation” OC).

The incidence was 1.4 fold (95% CI 0.9-2.3) increased in women with or without other risk factors for VTE and 1.5 fold (95% CI 0.8-2.7) increased in women with no other risk factors for VTE.

Epidemiological studies have also associated the use of combined oral contraceptives (COCs) with an increased risk for arterial (myocardial infarction, transient ischaemic attack, stroke) thromboembolism.

Extremely rarely, thrombosis has been reported to occur in other blood vessels e.g., hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

Symptoms of venous or arterial thrombosis can include:

- Unilateral leg pain, and/or swelling
- Sudden severe pain in the chest with possible radiation to the left arm
- Sudden breathlessness, sudden onset of coughing without a clear cause
- Any unusual, severe, prolonged headache
- Sudden partial or complete loss of vision
- Diplopia
- Slurred speech or aphasia
- Vertigo; collapse with or without focal seizure
- Weakness or very marked numbness suddenly affecting one side or one part of the body
- Motor disturbances
- ‘Acute’ abdominal pain

*The risk of venous thromboembolism in combined contraceptives users increases with:*

- Increasing age
- A positive family history (i.e. 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 hormonal contraceptive use
- Prolonged immobilisation, major surgery to the legs, or major trauma. In these situations it is advisable to discontinue use (in the case of elective surgery at least 4 weeks in advance) and not to resume until two weeks after complete remobilisation
- Obesity (body mass index over 30 kg/m²)
- Possibly also with superficial thrombophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the aetiology of venous thrombosis.

*The risk of arterial thromboembolic complications in combined contraceptives users increases with:*

- Increasing age;
- Smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- Dyslipoproteiniaemia;
- Obesity (body mass index over 30 kg/m²);
- Hypertension;
- Valvular heart disease;
- Atrial fibrillation;
- A positive family history (arterial thrombosis ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyper homocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

Other medical conditions, which have been associated with adverse circulatory events, included diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis).

The increased risk for thromboembolism in the puerperium must be considered (see section 4.6).

An increase in frequency or severity of headache (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of combination contraceptives.

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 compounding 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 combination 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 a combination hormonal contraceptive in pre-existing hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the combination hormonal contraceptive must be withdrawn. Combination 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; gallstones; porphyria; systemic 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 combination 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 combination 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 contraception. 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 contraindications (see section 4.3) and warnings (see section 4.4). The woman should also be instructed to carefully read the package leaflet and to adhere to the advice given.

The frequency and nature of subsequent examinations should be based on established guidelines and be adapted to the individual woman on the basis of clinical impression.

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

Bleeding irregularities

With all combination 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 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 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.

Herbal preparations containing St John's Wort (*Hypericum perforatum*) should not be used while taking EVRA (see section 4.5)

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

Influence of other medicinal products on EVRA

Medicinal product interactions, which result in an increased clearance of sex hormones can lead to breakthrough bleeding and hormonal contraceptive failure. This has been established with hydantoins, barbiturates, primidone, carbamazepine and rifampicin; bosentan, oxcarbazepine, topiramate, felbamate, ritonavir, griseofulvin, modafinil and phenyl butazone are also suspected. The mechanism of these interactions appears to be based on the hepatic enzyme inducing properties of these medicinal products. Maximal enzyme induction is generally not seen for 2-3 weeks but may be sustained for at least 4 weeks after cessation of therapy.

The herbal preparation of St John's Wort (*Hypericum perforatum*) should not be taken concomitantly with this medicinal product as this could potentially lead to a loss of contraceptive effect. Breakthrough bleeding and unintended pregnancies have been reported. This is due to induction of metabolising enzymes by St John's Wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's Wort.

Contraceptive failures have also been reported with antibiotics, such as ampicillin 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.

Women on treatment with any of these medicinal products should temporarily use a barrier method in addition to EVRA or choose another method of contraception. With microsomal enzyme-inducing medicinal products, the barrier method should be used during the time of concomitant administration of these medicinal products and for 28 days after their discontinuation. Women on treatment with antibiotics (except tetracycline) should use the barrier method until 7 days after discontinuation. If concomitant medicinal product administration runs beyond the 3 weeks of patch treatment, a new treatment cycle should be started immediately without having the usual patch-free interval.

For women on long-term therapy with hepatic enzyme inducers, another method of contraception should be considered.

Influence of EVRA on other medications

Progestogens and estrogens inhibit a variety of P450 enzymes (e.g., CYP 3A4, CYP 2C19) in human liver microsomes. However, under the recommended dosing regimen, the *in vivo* concentrations of norelgestromin and its metabolites, even at the peak serum levels, are relatively low compared to the inhibitory constant (Ki), indicating a low potential for clinical interaction. Nevertheless, physicians are advised to refer to prescribing information for recommendations regarding management of concomitant therapy, especially for agents with a narrow therapeutic index metabolised by these enzymes (e.g. cyclosporin).

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

Laboratory tests

Certain endocrine and liver function tests and blood components may be affected by hormonal contraceptives:

- Increased prothrombin and factors VII, VIII, IX and X; decreased anti-thrombin III; decreased protein S; increased norepinephrine (noradrenaline)-induced platelet aggregability.

- Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.

Other binding proteins may be elevated in serum.

Sex hormone-binding globulins (SHBG) are increased and result in elevated levels of total circulating endogenous sex steroids. However, the free or biologically active levels of sex steroids either decrease or remain the same.

High-density lipoprotein (HDL-C), total cholesterol (Total-C), low-density lipoprotein (LDL-C) and triglycerides may all increase slightly with EVRA, while LDL-C/HDL-C ratio may remain unchanged.

Glucose tolerance may be decreased.

Serum folate levels may be depressed by hormonal contraceptive therapy. This has potential to be of clinical significance if a woman becomes pregnant shortly after discontinuing hormonal contraceptives. All women are now advised to take supplemental folic acid peri-conceptionally.

## 4.6 Pregnancy and lactation

EVRA is not indicated during pregnancy.

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

For EVRA there are no clinical data on exposed pregnancies, which allow conclusions about its safety during pregnancy.

Studies in animals have shown reproductive toxicity (see section 5.3). On the basis of available data, a potential risk of masculinisation as a consequence of an exaggerated hormonal action cannot be excluded.

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

Lactation may be influenced by combination 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.

## 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

### 4.8.1 Clinical Trial Data

The most commonly reported adverse drug reactions (ADRs) in clinical trials were headache, nausea, and breast tenderness, occurring in approximately 21.0%, 16.6%, and 15.9% of patients, respectively.

Frequency estimate: 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).

| **System Organ Class** | **Adverse Drug Reactions in Clinical Trials** | | | | |
|---|---|---|---|---|---|
| | **Frequency** | | | | |
| | **Very common** | **Common** | **Uncommon** | **Rare** | **Very rare** |
| **Infections and infestations** | | Fungal infection (vaginal only), Vaginal candidiasis, Vulvovaginal mycotic infection | | | |
| **Metabolism and nutrition disorders** | | | Fluid retention, Hypercholesterolemia | | |
| **Psychiatric disorders** | | Depression, Mood altered, Mood swings | Affect lability, Anxiety, Insomnia, Libido decreased | Crying, Libido increased, Tearfulness | Aggression |
| **Nervous system disorders** | Headache | Dizziness, Migraine | | | |
| **Respiratory, thoracic and mediastinal disorders** | | | | Pulmonary embolism | |
| **Gastrointestinal disorders** | Nausea | Abdominal distension, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Vomiting, Diarrhoea | | | |
| **Hepatobiliary disorders** | | | | Cholecystitis | |

| | | | | | |
|---|---|---|---|---|---|
| **Skin and subcutaneous tissue disorders** | | Acne, Pruritus, Skin irritation | Dermatitis contact, Erythema | Chloasma | |
| **Musculoskeletal and connective tissue disorders** | | Muscle spasms | | | |
| **Reproductive system and breast disorders** | Breast tenderness | Breast discomfort, Breast enlargement, Breast pain, Dysmen-orrhoea, Menorrhagia, Metrorrhagia, Uterine spasm, Vaginal discharge | Breast disorder, Breast engorgement, Breast swelling, Fibrocystic breast disease, Galactorrhoea, Premenstrual syndrome, Vaginal haemorrhage, Vulvovaginal dryness | Genital discharge, Menstrual disorder, Menstruation irregular | Polymen-orrhoea |
| **General disorders and administration site conditions** | | Application site erythema, Application site irritation, Application site pruritus, Application site rash, Application site reaction, Fatigue, Malaise | Application site dermatitis, Application site discolouration, Application site hypersensitivity, Application site pain, Application site papules, Application site vesicles, Generalized oedema | Application site urticaria, Swelling | Applica-tion site oedema |
| **Investigations** | | Weight increased | Blood pressure increased, Blood triglycerides increased | Blood cholesterol increased | |

**4.8.2 Postmarketing Data**
**4.8.3**

Additional adverse drug reactions first identified during postmarketing experience with EVRA are listed below:

| | |
|---|---|
| **Infections and infestations** | Application site pustules, Rash pustular |
| **Neoplasms benign, malignant and unspecified (Incl cysts and polyps)** | Breast cancer, Breast cancer stage IV, Cervix carcinoma, Fibroadenoma of breast, Hepatic adenoma, Hepatic neoplasm, Uterine leiomyoma |
| **Immune system disorders** | Hypersensitivity |
| **Metabolism and nutrition disorders** | Hyperglycaemia, Insulin resistance |
| **Psychiatric disorders** | Anger, Emotional disorder, Frustration |
| **Nervous system disorders** | Basilar artery thrombosis, Brain stem infarction, Carotid artery occlusion, Cerebral artery embolism, Cerebral artery occlusion, Cerebral artery thrombosis, Cerebral haemorrhage, Cerebral infarction, Cerebral thrombosis, Cerebral venous thrombosis, Cerebrovascular accident, Embolic stroke, Haemorrhage intracranial, Haemorrhagic stroke, Intracranial venous sinus thrombosis, Ischaemic cerebral infarction, Ischaemic stroke, Lacunar infarction, Migraine with aura, Subarachnoid haemorrhage, Superior sagittal sinus thrombosis, Thromboembolic stroke, Thrombotic stroke, Transient ischaemic attack, Transverse sinus thrombosis |

| | |
|---|---|
| **Eye disorders** | Contact lens intolerance |
| **Cardiac disorders** | Acute myocardial infarction, Myocardial infarction |
| **Vascular disorders** | Arterial thrombosis, Arterial thrombosis limb, Axillary vein thrombosis, Budd-Chiari syndrome, Coronary artery thrombosis, Deep vein thrombosis, Embolism, Hepatic vein thrombosis, Hypertension, Hypertensive crisis, , Iliac artery thrombosis, Intracardiac thrombus, Jugular vein thrombosis, Mesenteric vein thrombosis, Pelvic venous thrombosis, Peripheral embolism, Portal vein thrombosis, Renal embolism, Renal vein thrombosis, Retinal artery occlusion, Retinal vascular thrombosis, Retinal vein occlusion, Splenic vein thrombosis, Superficial thrombophlebitis, Thrombophlebitis, Thrombosis, Vena cava thrombosis, Venous thrombosis, Venous thrombosis limb |
| **Respiratory, thoracic and mediastinal disorders** | Pulmonary artery thrombosis, Pulmonary thrombosis |
| **Gastrointestinal disorders** | Colitis |
| **Hepatobiliary disorders** | Cholelithiasis, Cholestasis, Hepatic lesion, Jaundice cholestatic |
| **Skin and subcutaneous tissues disorders** | Alopecia, Angioedema, Dermatitis allergic, Eczema, Erythema multiforme, Erythema nodosum, Exfoliative rash, Photosensitivity reaction, Pruritus generalised, Rash, Rash erythematous, Rash pruritic, Seborrhoeic dermatitis, Skin reaction, Urticaria |
| **Reproductive system and breast disorders** | Amenorrhoea, Breast mass, Cervical dysplasia, Hypomenorrhoea, Menometrorrhagia, Oligomenorrhoea, Suppressed lactation |
| **General disorders and administration site conditions** | Application site abscess, Application site anaesthesia, Application site atrophy, Application site bleeding, Application site bruising, Application site burn, Application site discharge, Application site discomfort, Application site dryness, Application site eczema, Application site erosion, Application site excoriation, Application site exfoliation, Application site induration, Application site infection, Application site inflammation, Application site mass, Application site nodule, Application site odour, Application site paraesthesia, Application site photosensitivity reaction, Application site scab, Application site scar, Application site swelling, Application site ulcer, Application site warmth, Face oedema, Irritability, Localised oedema, Oedema peripheral, Pitting oedema |
| **Investigations** | Blood cholesterol abnormal, Blood glucose abnormal, Blood glucose decreased, Low density lipoprotein increased |
| **Injury, poisoning and procedural complications** | Contact lens complication |

## 4.9 Overdose

Serious ill effects have not been reported following accidental ingestion of large doses of oral contraceptives. Overdosage 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: Norelgestromin and estrogen; ATC-code: G03AA13.

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.

**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 | 5831 | 4592 | 5095 | 4005 | 21,669 |
| Overall Pearl Index (95% CI) | 0.73 (0.15,1.31) | 0.89 (0.02,1.76) | 0.57 (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 (0,1.42) | 0.28 (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=3319) 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 Pharmacokinetic Properties, Special Populations), 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 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 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 patch, the mean elimination half-lives of norelgestromin and ethinyl estradiol were approximately 28 hours and 17 hours, respectively. The metabolites of norelgestromin and ethinyl estradiol are eliminated by renal and fecal pathways.

Transdermal versus Oral Contraceptives

The pharmacokinetic profiles of transdermal and oral combined hormonal contraceptives are different and caution should be exercised when making a direct comparison of these PK parameters.
In a study comparing EVRA to an oral contraceptive containing norgestimate (parent drug of norelgestromin) 250 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 Pre-clinical safety data

Preclinical 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

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.

### 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.

### 6.6 Special precautions for disposal and other handling

Apply immediately upon removal from the protective sachet. After use the patch still contains substantial quantities of active ingredients. Remaining hormonal active ingredients of the patch may have harmful effects if reaching the aquatic environment. Therefore, the used patch should be discarded carefully. The disposal label from the outside of the sachet should be peeled open. The used 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 patch within. Any used or unused patches should be discarded according to local requirements or returned to the pharmacy. Used patches should not be flushed down the toilet nor placed in liquid waste disposal systems.

## 7. MARKETING AUTHORISATION HOLDER

JANSSEN-CILAG INTERNATIONAL N.V.
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 authorization: 22 August 2002.
Date of latest renewal: 26 August 2007.

## 10. DATE OF REVISION OF THE TEXT

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

# ANNEX II

## A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

## B. CONDITIONS OF THE MARKETING AUTHORISATION

## A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

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

Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse, Belgium

## B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

The MAH will continue to submit yearly PSURs unless otherwise specified by the CHMP

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**BOX OF 3 PATCHES**
**BOX OF 9 PATCHES**
**BOX OF 18 PATCHES**

## 1. NAME OF THE MEDICINAL PRODUCT

EVRA transdermal patch

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

1 patch releases: 150 micrograms norelgestromin and 20 micrograms ethinyl estradiol per 24 hours

## 3. LIST OF EXCIPIENTS

Other ingredients: polyisobutylene, polybutene, lauryl lactate, crospovidone, non-woven-polyester fabric

## 4. PHARMACEUTICAL FORM AND CONTENTS

3 transdermal patches
9 transdermal patches
18 transdermal patches

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use

Read the package leaflet before use

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

Keep out of the reach and sight of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original sachet and carton
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

Marketing Authorisation holder:
Janssen-Cilag International N.V.
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

**MINIMUN PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**
**SACHET LABEL**

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

EVRA transdermal patch

## 2. METHOD OF ADMINISTRATION

Transdermal use

Read the package leaflet

## 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 transdermal patch**
**Norelgestromin and ethinyl estradiol**

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


## 1. What EVRA is and what it is used for

The name of your medicine is EVRA transdermal patch. It is called 'EVRA' in this leaflet.
It is used to prevent pregnancy.
EVRA contains two types of hormones:
- norelgestromin
- ethinyl estradiol

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

## 2. Before you use EVRA

**Do not use EVRA if:**
- You are allergic (hypersensitive) to norelgestromin, ethinyl estradiol or any of the other ingredients in EVRA (listed in Section 7 below)
- You have ever had a heart attack or a type of chest pain called 'angina'
- You have ever had a stroke or signs which may lead to stroke. This includes a slight, temporary stroke, without any after effects
- You have high blood pressure (160/100 mmHg or above)
- You have diabetes with damaged blood vessels
- You have bad headaches with neurological symptoms such as changes in vision or numbness in any part of your body (migraine with focal aura)
- You have ever had a blood clot (thrombosis) in your legs (deep vein thrombosis or DVT) or lungs (pulmonary embolism) or another part of your body
- You have an illness which runs in your family which affects the clotting of your blood (called 'protein C deficiency' or 'protein S deficiency')
- You have very high fat levels in your blood (cholesterol or triglycerides)
- You have an illness which runs in your family which affects fat levels in your blood (called dyslipoproteinemia)
- You have ever had liver tumours or any problem with your liver
- You have ever been told you might have breast cancer or cancer of the womb, cervix or vagina
- You have unexplained vaginal bleeding.

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

**Take special care with EVRA**

**Medical check-ups**
Before using EVRA, you will need to see your doctor for a medical check-up.

Check with your doctor or pharmacist before using EVRA if you have any of the following or they happen or get worse while using EVRA:
- You weigh 90 kg (which is 14 stone 2 lb) or more
- You, or any of your family, have high fat levels in the blood (triglycerides or cholesterol)
- You have high blood pressure or your blood pressure gets higher
- You have a blood problem called porphyria
- You have an immune system problem called 'SLE' (systemic lupus erythematosus)
- You have a blood problem which causes liver damage called 'HUS' (haemolytic uremic syndrome)
- You have a hearing loss
- You have epilepsy or any other problem that can cause fits (convulsions)
- You have a problem of the nervous system involving sudden movements of the body called 'Sydenham's chorea'
- You have diabetes
- You have depression
- You have gallstones
- You have liver problems including yellowing of the skin and whites of the eye (jaundice)
- You have an inflammatory illness of your gut (Crohn's disease or ulcerative colitis)
- You had a skin rash with blisters during pregnancy (called 'herpes gestationis')
- You have 'pregnancy spots'. These are yellowish-brown patches or spots, especially on your face (called 'chloasma')
- You think you might be pregnant.

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

**Taking other medicines:**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

**Certain medicines and herbal remedies may stop EVRA from working properly. If this happens you could get pregnant.**
Tell your doctor if you are taking:
- Medicines for HIV infection such as ritonavir
- Medicines for infection such as ampicillin, rifampicin, griseofulvin and tetracycline
- Medicines for epilepsy such as topiramate, barbiturates, phenyl butazone, phenytoin sodium, carbamazepine, primidone, hydantoins, oxcarbamazepine and felbamate
- Bosentan - used for high blood pressure in the lung arteries (pulmonary arterial hypertension)
- Modafinil - used for enhancing mood
- St. John's Wort - an herbal remedy used for depression.

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.

If you take lamotrigine, a medicine for epilepsy, EVRA may stop it from working properly. This can increase the risk of fits (seizures). Your doctor may need to change
your dose of lamotrigine.
Ask your doctor or pharmacist for advice before taking any medicine.

**Using EVRA with food and drink**
It is not expected that food or drink will affect the way EVRA works.

**Pregnancy and breast-feeding**
- Do not use EVRA if you are pregnant or think you may be pregnant
- Do not use EVRA if you are breast-feeding or planning to breast-feed.

Ask your doctor or pharmacist for advice before taking any medicine during pregnancy or while breast-feeding.

**Driving and using machines**
You can drive or operate machinery while using EVRA.

**Sexually transmitted disease**
EVRA 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**
- Tell your doctor or the person taking the sample, if you are having a blood or urine test. This is because EVRA may affect some results of the tests.

## 3. 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 blood clots (thrombosis)**
Using combined hormonal contraceptives, including EVRA, increases the chances of getting a thrombosis (blood clots). It is possible that the risk of blood clots in the legs and/or lungs with EVRA is more than the risk with combined birth control pills. This risk of developing blood clots is not affected by how long you use the medicine. The risk returns to normal, a few months after you stop using the medicine.

Blood clots can cause a blockage in a vein or artery and this may make you permanently disabled or even cause death.
- Blood clots can form in a vein in your leg (deep vein thrombosis or DVT) and travel to the lungs. This can cause chest pain and make you breathless or collapse. This is called a 'pulmonary embolism' or PE
- Very rarely, blood clots can form in the blood vessels of the heart (causing a heart attack) or the brain (causing a stroke)
- In extremely rare cases, blood clots can happen in other places such as the liver, gut, kidney or eye. Blood clots in the eye may cause loss of eyesight or double vision.

**Tell your doctor immediately if you notice any possible signs of a blood clot, such as:**
- Pain or swelling in either leg
- Pain in the chest, which may spread to the arm
- Sudden shortness of breath or sudden coughing
- Unusual, severe or long-lasting headache
- Vision problems
- Difficulty speaking
- Feeling dizzy or fainting spells

- Feeling weak or numb on one side or one part of the body
- Difficulty walking or holding things
- Sudden stomach pain

If you think you might have any of these, talk to your doctor immediately.

**Your chance of getting a blood clot increases:**
- As you get older
- If blood clots in blood vessels (veins or arteries) runs in the family
- If you smoke, especially if you are over 35 years of age
- If you stay in bed for many days
- If you are very overweight
- If you have just had a baby, miscarriage or abortion
- If you have had a serious injury, particularly of the leg or hip
- If you have had or are going to have a major operation or need to have bed rest for a long time.

Normally you should not use EVRA for two weeks before or two weeks after surgery
- If you have ever had blood clots before
- If you have problems with your blood fats (cholesterol or triglycerides)
- If you have high blood pressure
- If you have heart problems (problems with heart valves, abnormal heart rhythm).

**Combined hormonal contraceptives and cancer**
**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.

**Cervical cancer**
Cervical cancer also has been found more often in women taking combined hormonal contraceptives. However, this may be due to other causes. These include more sexual partners and sexually transmitted disease.

**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.**

## 4. How to use EVRA

Always use EVRA exactly as described in this leaflet.
- 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.

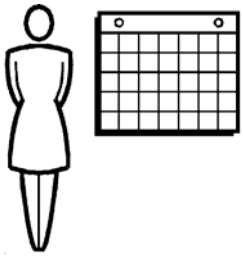
Talk to your doctor about using EVRA after having a baby or after an abortion or miscarriage.

**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.

**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

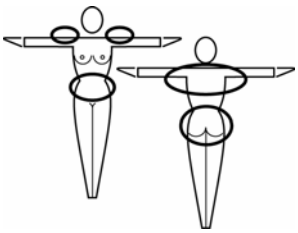
- Only wear one patch at a time
- Do not put the patch on skin that is red, irritated or cut
- To work properly the patch must stick firmly to your skin
- Press the patch down firmly until the edges stick well
- Do not use creams, oils, lotions, powder or makeup on the skin where you are placing a patch 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**.

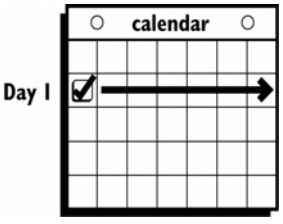
Using your fingers, open the foil sachet

- 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

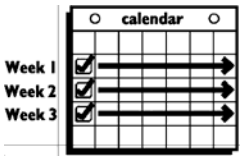
- Then take off the other half of the covering
- Press down firmly on the patch with the palm of your hand for 10 seconds
- Make sure that the edges stick well.




Wear the patch for 7 days (one week)

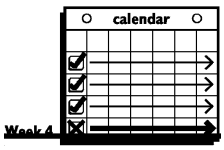
- On the first "Patch Change Day", Day 8, take off the used patch
- Put on a new patch immediately.

- On Day 15 (Week 3), take off the used patch



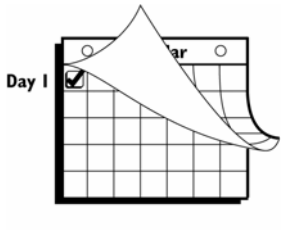

- Put on another new one.

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.

**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 or another healthcare professional at the clinic. 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 switch from the oral contraceptive pill to EVRA**

If you are switching from an oral contraceptive pill to EVRA:

- 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 EVRA.

**If you switch from the mini-pill to EVRA**

- You may start EVRA any day after stopping the mini-pill
- The first day after stopping the mini-pill, put on a patch
- Use a non-hormonal contraceptive until Day 8, when you change your patch.

**If you have absent or irregular bleeding with EVRA**

EVRA 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 EVRA 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 EVRA 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 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 bleeding. This usually happens in the first 3 months and especially if your periods were not regular before you started using EVRA.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

## 5. Possible side effects

Like all medicines, EVRA can cause side effects although not everybody gets them.
Tell your doctor if you notice any unwanted effects. If you think that you have a serious side effect when using EVRA, take off the patch and speak to your doctor or pharmacist immediately. In the meantime, you should use another method of contraception.

Serious side effects associated with combined hormonal contraceptives are described in Section 3 above ("Risks of using combined hormonal contraceptives"). Please read this section for additional information.

**Very common side effects (affects more than 1 in 10 women):**
- Headache
- Feeling sick (nausea)
- Breast tenderness.

**Common side effects (affects less than 1 in 10 women):**
- Vaginal yeast infection, sometimes called thrush
- Mood problems such as depression, change in mood or mood swings
- Feeling dizzy
- Migraine
- Stomach pain or bloating
- Being sick (vomiting) or diarrhoea
- Acne, skin itching or skin irritation
- Muscle spasms
- Breast pain or enlargement
- Uterine cramps, painful or heavy periods, bleeding between periods or 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 (affects less than 1 in 100):**
- Swelling due to water retention in the body
- High levels of fats in the blood (such as cholesterol or triglycerides)
- Uncontrollable emotions
- Anxiety
- Problems sleeping (insomnia)
- Less interest in sex
- Skin rash, redness of the skin
- Swelling of the breasts, lumps in the breast or abnormal breast milk production
- Premenstrual syndrome
- Vaginal bleeding or dryness
- Problems where the patch has been on the skin (such as swelling, discoloured skin, pain, spots, blisters or the skin feeling over-sensitive)
- Swelling
- Rise in blood pressure.

**Rare side effects (affects less than 1 in 1000 women):**
- Abnormal crying
- Increased interest in sex
- Blood clot in the lung
- Inflammation of the gall bladder
- Yellow-brown pigment spots on the face
- Irregular periods
- A bumpy rash (hives) where the patch has been on the skin
- Rise in cholesterol levels.

**Very rare side effects (affects less than 1 in 10,000 women):**
- Aggression
- Having more periods than normal.

**Other side effects include:**
- Other problems where the patch has been on the skin, skin reactions or allergic reactions
- Non-cancerous (benign) tumours in your breast or liver
- Breast, cervical or liver cancer
- Fibroids in the womb (uterus)
- Abnormal blood sugar, cholesterol or insulin levels
- Blood clots, blocked arteries, heart attack or stroke
- Problems when wearing contact lenses
- High blood pressure
- Inflammation of the colon
- Gallstones or blockage of the bile duct
- Yellowing of the skin and whites of the eyes
- Hair loss
- Sensitivity to sunlight
- Less frequent, light or no periods
- Anger, feeling irritable or frustrated.

**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.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 6. How to store EVRA

Keep out of the reach and sight of children.
Store in the original container to protect from light and moisture.
Do not refrigerate or freeze.
Do not use EVRA after the expiry date, which is stated on the label. The expiry date refers to the last day of that month.

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.

Used patches should not be flushed down the toilet or placed in liquid disposal systems. Ask your pharmacist how to dispose of any patches no longer required. These measures will help to protect the environment.

## 7. Further information

**What EVRA contains**

**The active substances** in EVRA are norelgestromin 6mg and ethinyl estradiol 600 micrograms. The active substances are released over 7 days with 150 micrograms norelgestromin and 20 micrograms ethinyl estradiol being released each 24 hours.

**The other ingredients** in the patch are polyisobutylene, polybutene, crospovidone, non-woven polyester fabric and lauryl lactate.

**What EVRA looks like and contents of the pack**
EVRA is a thin, beige, plastic transdermal patch. 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.

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

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

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

**België/Belgique/Belgien**
JANSSEN-CILAG N.V./S.A.
Roderveldlaan 1
B-2600 Berchem
Tél/Tel: + 32 3 280 54 11

**Luxembourg/Luxemburg**
JANSSEN-CILAG N.V./S.A.
Roderveldlaan 1
B-2600 Berchem
Tél: +32 3 280 54 11

**България**
Johnson & Johnson d.o.o.
Бизнес Парк София,
Младост 4, сграда 4, етаж 3
София 1715
Тел.: +359 2 489 94 00 (05)

**Magyarország**
JANSSEN-CILAG Kft.
H-2045 Törökbálint, Tó Park
Tel. : +36 23 513-800

**Česká republika**
JANSSEN-CILAG s.r.o.
Karla Engliše 3201/6
CZ-150 00 Praha 5
Tel. +420 227 012 222

**Malta**
A.M.Mangion Ltd
Triq Ġdida fi Triq Valletta
Luqa LQA 6000
Malta
tel:+356 2397 6000

**Danmark**
JANSSEN-CILAG A/S
Hammerbakken 19
Postboks 149
DK-3460 Birkerød
Tlf: +45 45 94 82 82

**Deutschland**
JANSSEN-CILAG GmbH
Raiffeisenstr. 8
D-41470 Neuss
Tel: +49 2137-955- 955

**Eesti**
Janssen-Cilag Polska Sp.z o.o.
Eesti filiaal
Lõõtsa 2
EE-11415 Tallinn
Tel: +372 617 7410

**Ελλάδα**
JANSSEN-CILAG Φαρμακευτική Α.Ε.Β.Ε.
Λεωφόρος Ειρήνης 56
GR-151 21 Πεύκη, Αθήνα
Τηλ: +30 210 61 40 061

**España**
JANSSEN-CILAG, S.A.
Paseo de las Doce Estrellas, 5-7
Campo de las Naciones
E-28042 Madrid
Tel: +34 91 722 81 00

**France**
JANSSEN-CILAG
1, rue de Camille Desmoulins
TSA 91003
F-92787 Issy Les Moulineaux Cedex 9
Tel: 0800 25 50 75 or
+ 33 1 55 00 44 44

**Ireland**
JANSSEN-CILAG Ltd.
50-100 Holmers Farm Way
High Wycombe
UK - HP12 4EG Buckinghamshire
Tel: +44 1 494 567 567

**Ísland**
JANSSEN-CILAG AB
c/o Vistor hf.
Hörgatún 2
IS-210 Garðabær
Iceland
tel. (+354) 535 7000

**Nederland**
JANSSEN-CILAG B.V.
Postbus 90240
NL-5000 LT Tilburg
Tel: +31 13 583 73 73

**Norge**
JANSSEN-CILAG A.S.
Hoffsveien 1 D
N- 0275 Oslo
Tlf: + 47 24 12 65 00

**Österreich**
JANSSEN-CILAG Pharma GmbH.
Pfarrgasse 75
A-1232 Wien
Tel:+43 1 610 300

**Polska**
JANSSEN–CILAG Polska Sp. z o.o., ul. Iłżecka 24,
PL- 02-135 Warszawa
Tel.: + 48 22 –237 60 00

**Portugal**
JANSSEN-CILAG FARMACÊUTICA, LDA
Estrada Consiglieri Pedroso, 69 A
Queluz de Baixo
2734-503 Barcarena
Tel: +351 21-4368835

**România**
Johnson & Johnson d.o.o. Rep.Office Janssen-Cilag
Str. Tipogrfilor nr.11 - 15
013714Bucureşti
Tel: +4 0212071800

**Slovenija**
Johnson & Johnson d.o.o.
Šmartinska cesta 53
Sl-1000, Ljubljana
Tel. + 386 1 401 18 30

**Slovenská republika**
Johnson&Johnson s.r.o.
Plynárenská 7/B
SK- 824 78 Bratislava 26
tel. +421 233 552 600

**Italia**
JANSSEN-CILAG SpA
Via M.Buonarroti, 23
I-20093 Cologno Monzese MI
Tel: +39 02/2510.1

**Κύπρος**
Βαρνάβας Χατζηπαναγής Λτδ
7 Ανδροκλέους
CY-1060 Λευκωσία
Τηλ: +357 22 755 214

**Latvija**
Janssen-Cilag Polska Sp. z o.o.
filiāle Latvijā
Matrožu iela 15
Rīga, LV-1048
Tel: + 371 678 93561

**Lietuva**
UAB „Johnson & Johnson“
Geležinio Vilko g. 18A
LT-08104 Vilnius
Tel: +370 5 278 68 88

**Suomi/Finland**
JANSSEN-CILAG OY
Metsänneidonkuja/Skogsjungfrugränden 8
FI-02130 Espoo/Esbo
Puh/Tel: +358 9 4155 5300

**Sverige**
JANSSEN-CILAG AB
Box 7073
SE-192 07 Sollentuna
Tel: +46 8 626 50 00

**United Kingdom**
JANSSEN-CILAG Ltd.
50-100 Holmers Farm Way
High Wycombe
UK - HP12 4EG Buckinghamshire
Tel: +44 1 494 567 567

**This leaflet was last approved in**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.