PROFESSIONAL INFORMATION (PI)

SCHEDULING STATUS

Schedule 3

1 NAME OF THE MEDICINE

EVRA® (Transdermal Patch)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

EVRA is a combination transdermal contraceptive patch with a contact surface area of 20 cm^2. It contains 6 mg norelgestromin (NGMN) and 600 micrograms of ethinyloestradiol (EE); and is designed to provide continuous delivery of NGMN and EE into the bloodstream over a seven-day duration of wear (see *section 5.2*).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Transdermal patch.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EVRA is indicated for the prevention of pregnancy.

4.2 Posology and method of administration

Posology

To achieve maximum contraceptive effectiveness EVRA must be used exactly as directed.

One patch should be worn at a time. The EVRA patch should not be cut, damaged or altered in any way. If the EVRA patch is cut, damaged or altered in size, contraceptive efficacy may be impaired.

Contraception with EVRA begins on the first day of menses. 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 and 22 and Day 1 of the next cycle).

A single patch is applied and worn for one full week (7 days).

Each used patch is removed and immediately replaced by 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 the patch-free week; the next EVRA patch should be applied even if there has been no bleeding or if the 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 coital exposure has occurred during such an extended patch-free interval, the possibility of fertilisation should be considered.

Special populations:

Children

Safety and efficacy of EVRA was established in women from 18 years of age. Safety and efficacy are expected to be the same for postpubertal adolescents and the same dosage is recommended in these subjects. Use of EVRA before menarche is not indicated.

Elderly

Not intended for use by post-menopausal women.

Renal impairment

EVRA has not been studied in women with renal impairment. No dose adjustment is necessary but there is a suggestion in the literature that the unbound fraction of EE (ethinyloestradiol) is higher. EVRA should be used with supervision in this population.

Hepatic impairment

EVRA is contraindicated in this population.

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 EVRA 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.

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

The patch should be pressed down firmly until the edges stick well. To prevent interference with the adhesive properties of EVRA, no make-up, creams, lotions, powders or other topical products should be applied to the skin area where the EVRA patch is currently placed or will be applied shortly.

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

Instructions for use/handling: Apply immediately upon removal from the protective sachet. After removing the worn patch, the used patch should be folded in half, adhesive side together so that the release membrane is not exposed. The folded patch should be placed in a sturdy container, preferably with a child-resistant cap, and the container disposed of in the trash. Keep out of reach of children.

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 contraception 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 lifted or became 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.

EVRA should not be re-applied if it is no longer sticky, if it has become stuck to itself or another surface, if it has other material stuck to it or if it has become loose or fallen off before. If a patch cannot be re-applied, a new patch should be applied immediately. Supplemental adhesives or wraps 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 her new cycle as soon as remembered. There is now a new "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 coital exposure has occurred during such an extended patch-free interval, the possibility of pregnancy should be considered.

- **in the middle of the patch 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". 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 patch 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 be started on the usual

"Change Day", which is the day after Day 28. No additional contraceptive use is required.

Change Day Adjustment

If the patient wishes to move her 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.

Switching from an oral 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 start of treatment with EVRA. If therapy starts after the first day of withdrawal bleeding, a non-hormonal contraceptive should be used concurrently for 7 days.

If more than 7 days elapse after taking the last active oral contraceptive tablet, the patient may have ovulated. The patient should be instructed to consult her medical practitioner before initiating treatment with EVRA. If coital exposure has occurred during such an extended patch-free interval, the possibility of pregnancy should be considered.

Use after childbirth

Users who elect not to breastfeed should start contraceptive therapy with EVRA no sooner than 4 weeks after childbirth. (See*: section 4.6* and *Thromboembolic and Other Vascular Problems under section 4.4*).

Use after 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 or before day 21 post-abortion (at 20 weeks gestation) is not known.

Breakthrough bleeding or spotting

In the event of breakthrough bleeding or spotting (bleeding that occurs during EVRA usage), treatment should be continued. This type of bleeding usually disappears after the first few cycles. If breakthrough bleeding persists for more than one cycle or lasts for more than a few days, talk to your healthcare professional, a cause other than EVRA should be considered.

In the event of no withdrawal bleeding (bleeding that should occur during the patch-free week), treatment should be continued on the next scheduled Change Day. If EVRA has been used correctly, the absence of withdrawal bleeding is not necessarily an indication of pregnancy. Nevertheless, the possibility of pregnancy should be ruled out if absence of withdrawal bleeding occurs in 2 consecutive cycles.

Vomiting or diarrhoea

Dose delivery by transdermal application should be unaffected by vomiting or diarrhoea.

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.

4.3 Contraindications

EVRA should not be used with:

- Hypersensitivity, systemic reactions or severe local reactions to any of the components of EVRA i.e. norelgestromin, ethinyloestradiol, polyisobutylene, polybutene, crospovidone, non-woven polyester fabric and lauryl lactate
- Current or previous arterial or venous thrombotic or embolic processes e. g. deep vein thrombosis, retinal thrombosis, pulmonary embolism, cerebrovascular accident, myocardial infarction, thrombophlebitis or significantly predisposing conditions such as arterial fibrillation and significant cases of structural heart disease (see *section 4.4 - Thromboembolic and other Vascular Disorders*)
- Known thrombophilic conditions predisposed to arterial or venous thrombosis (thrombophilia)
- Migraine
- Porphyria
- Previous pemphigus gestationis
- Uncontrolled hypertension (persistent values of ≥ 160+/100+ mm Hg)
- Diabetes with vascular involvement
- Benign intracranial hypertension (pseudotumour cerebrii)
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected oestrogen-dependent neoplasia

- Steroid-dependent jaundice, cholestatic jaundice, history of jaundice of pregnancy
- Abnormal liver function related to acute or chronic hepatocellular disease
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy
- Undiagnosed abnormal genital bleeding
- Patients receiving drug combinations with paritaprevir/ritonavir, ombitasvir, and/or dasabuvir due to potential for ALT elevations.

4.4 Special warnings and precautions for use

Smoking and age

Cigarette smoking increases the risk of serious cardiovascular events from EVRA use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, EVRA should not be used by women who are over 35 years of age and smoke.

Body Weight (≥ 90 kg)

EVRA may be less effective in women with body weight ≥ 90 kg than in women with lower body weights. Below 90 kg there was no association between body weight and pregnancy

General

In case of undiagnosed, persistent or recurrent vaginal bleeding, appropriate measures should be taken to rule out malignancy.

When EVRA was used correctly in clinical trials, the chance of becoming pregnant was less than 1 % in the first year of use. The chance of becoming pregnant increases with dosing errors.

***Pre-existing conditions*:**

When weighing the risks/benefits of hormonal contraceptive use, the medical practitioner should be familiar with the following conditions that may increase the risk of complications associated with hormonal contraceptive use:

- Conditions which increase the risk of developing venous thromboembolic conditions, e.g. prolonged immobilisation or major surgery, leg surgery or a leg cast, obesity, family history of thromboembolic disease
- Risk factors for arterial disease, e.g. smoking, hyperlipidaemia, hypertension (persistent blood pressure values ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) or obesity
- Severe migraine without aura
- Diabetes mellitus
- Severe depression or a history of this condition
- Presence or history of cholelithiasis
- Chronic idiopathic jaundice
- Otosclerosis
- Family history of cholestatic jaundice (e.g. Rotor, Dubin-Johnson Syndrome)

Psychiatric Disorders

Mood changes and depression are side effects reported with the use of hormonal contraceptives including EVRA®. There is some evidence that hormonal contraceptive use may be associated with severe depression and a higher risk of suicidal thoughts/behavior (e.g. talking about suicide, withdrawing from social contact, having mood swings, being preoccupied

with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs, doing self-destructive things, personality changes) and suicide. Prescribers should inform their patients to contact their doctor for advice if they experience mood changes and depression whilst on treatment with EVRA® (see section 4.8).

Thromboembolic and other vascular disorders

An increased risk of thromboembolic and thrombotic disease that could lead to permanent disability or death has been associated with the use of hormonal contraceptives and is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1,5 to 6 for users with predisposing conditions for venous thromboembolic disease. Studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4,5 for new cases requiring hospitalisation.

The risk of thromboembolic disease associated with EVRA returns to baseline after the combined hormonal contraceptive use is stopped. Venous thromboembolism (VTE) risk is highest in the first ever year of use. There is also some evidence that the risk of VTE when a combined hormonal contraceptive (CHC) is restarted after ≥ 4 weeks of discontinuation is at least as high as the risk of VTE when a CHC is initially started.

The healthcare provider should be alert to the earliest manifestations of thromboembolic disorders. Should any of these occur or be suspected, EVRA should be discontinued immediately.

A two to four-fold increase in the relative risk of post-operative thromboembolic complications has been reported with the use of hormonal contraceptives. The relative risk of venous thrombosis in

users who have predisposing conditions is twice that of users without such medical conditions. If feasible, hormonal contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilisation. Since the immediate postpartum or post-abortion period is also associated with an increased risk of thromboembolism, hormonal contraceptives should be started as described in Sections: *Use After Childbirth and Use After Abortion or Miscarriage.*

The relative risk of arterial thrombosis is increased by the presence of other predisposing factors such as cigarette smoking (particularly after the age of 35 years), hypertension, hypercholesterolaemia, obesity, diabetes, history of pre-eclamptic toxaemia and increasing age. Hormonal contraceptives have been associated with these serious vascular complications.

Users of hormonal contraceptives should be strongly advised not to smoke.

Due to the vague symptomatology of many thromboembolic events, EVRA should be discontinued in cases of suspected thromboses while diagnostic interventions are being pursued.

There have been clinical reports of retinal thrombosis associated with the use of EVRA. EVRA should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilloedema or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

Hypertension

An increase in blood pressure (BP) has been reported in some users taking EVRA. Studies indicate that this increase is more likely to occur in older EVRA users and with extended

duration of use. For many users, elevated blood pressure will return to normal after they stop taking EVRA. There is no difference in the occurrence of hypertension between former and never users.

Users with hypertension should have their condition under control before EVRA contraceptive therapy can be started. EVRA therapy should be discontinued if significant persistent elevation of blood pressure (≥ 160 mm Hg systolic or ≥ 100 Hg diastolic) occurs and cannot be adequately controlled. In general, women who develop hypertension during hormonal contraceptive therapy should be switched to a non-hormonal contraceptive. If other contraceptive methods are not suitable hormonal contraceptive therapy may continue combined with antihypertensive therapy. Regular monitoring of BP throughout hormonal contraceptive therapy, such as EVRA, is recommended.

Hepatobiliary disease

Benign hepatic adenomas are associated with combination hormonal contraceptive use. Indirect calculations have estimated the attributable risk to be in the range of 3,3 cases /100 000 for users, a risk that increases after 4 or more years of use, especially with hormonal contraceptives containing 50 micrograms or more of oestrogen. Rupture of benign hepatic adenomas may cause death through intra-abdominal haemorrhage.

Studies have shown that EVRA users have an increased risk of developing hepatocelluar carcinoma.

Gallbladder disease including cholecystitis and cholelithiasis has been reported with hormonal contraceptive use.

Carcinoma of the reproductive organs and breasts

Studies have reported an increased risk of developing breast cancer, particularly at a younger age. This increased risk has been reported to be related to duration of use, before the first term of pregnancy.

A meta-analysis of 54 epidemiological reports that users who are currently using combined hormonal contraceptives or have used them in the past 10 years are at an increased risk of having breast cancer.
The increase in risk of breast cancer should be discussed with the users.

Hormonal contraceptive use has been associated with an increased risk of cervical intraepithelial neoplasia. 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.

Metabolic effects

EVRA may cause a decrease in glucose tolerance. This effect has been shown to be directly related to oestrogen dose.

Progestogens increase insulin secretion and create insulin resistance. This effect varies with different progestational agents. However, in the non-diabetic woman, hormonal contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, pre-diabetic and diabetic users in particular should be monitored carefully while using hormonal contraceptives.

Increases in serum triglycerides and lipoprotein levels have been reported in hormonal contraceptive users.

Headache

The following events require discontinuation of EVRA and evaluation of the cause: onset or exacerbation of migraines with or without focal aura; or development of headaches with a new pattern that is recurrent, persistent or severe.

Bleeding irregularities

Breakthrough bleeding, spotting and/or amenorrhoea may be encountered in users on EVRA, especially during the first 3 months of use. Non-hormonal causes should be considered and, if necessary, adequate diagnostic measures taken to rule out organic disease or pregnancy.

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

Chloasma

Chloasma may occur with use of EVRA, 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.

Transdermal versus oral contraceptives

Prescribers should be aware of the differences in pharmacokinetic (PK) profiles of transdermal and oral combined hormonal contraceptives and should exercise caution when making a direct comparison between these parameters. EVRA is designed to maintain steady delivery of EE and NGMN over a seven-day period while oral contraceptives are administered on a daily basis

and produce daily peaks and troughs. Inter-subject variability (% CV) for PK parameters following delivery from a patch such as EVRA is higher relative to the variability determined from the oral contraceptive. The clinical relevance of the differences in PK profiles between transdermal and oral delivery is not known (see *section 5.2*).

4.5 Interaction with other medicines and other forms of interaction

Changes in contraceptive effectiveness associated with co-administration of other medicines:

If a woman on EVRA takes a medicine or herbal product that induces enzymes, including CYP3A4, that metabolise contraceptive hormones, she should be counseled to use additional contraception or a different method of contraception. Medicines or herbal products that induce such enzymes may decrease the plasma concentrations of EVRA and may decrease the effectiveness of EVRA or increase breakthrough bleeding. Some medicines or herbal products that may decrease the effectiveness of EVRA include:

- some anti-epileptics (e.g. carbamazepine, eslicarbazine acetate, felbamate, oxcarbazepine, phenytoin, rufinamide, topiramate
- (fos)aprepitant
- barbiturates
- bosentan
- griseofulvin
- some (combinations of) HIV protease inhibitors (e.g. nelfinavir, ritonavir, ritonavir-boosted protease inhibitors)
- medications given in combination with HIV/AIDS drugs (e.g. cobicistat)
- modafinil
- some non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine)

- rifampin and rifabutin
- St. John's Wort

Management

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

Short-term

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

Long-term

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

Increase in plasma hormone levels associated with co-administered medicines:

Some medicines and grapefruit juice may increase the plasma levels of ethinyloestradiol if co-administered. Examples include:

- paracetamol
- ascorbic acid
- CYP3A4 inhibitors (including itraconazole, ketoconazole, voriconazole, fluconazole and grapefruit juice)

- etoricoxib
- some HIV protease inhibitors (e.g. atazanavir, indinavir)
- HMG-CoA reductase inhibitors (including atorvastatin and rosuvastatin)
- some non-nucleoside reverse transcriptase inhibitors (e.g. etravirine)

Changes in plasma levels of co-administered medicines:

Data from oral combination hormonal contraceptives indicate that they may also affect the pharmacokinetics of some other medicines if used concomitantly.

Examples of medicines whose plasma levels may be increased (due to CYP inhibition) include:

- ciclosporin
- omeprazole
- prednisolone and prednisone
- selegiline
- theophylline
- tizanidine
- voriconazole

Examples of medicines whose plasma levels may be decreased (due to induction of glucuronidation) include:

- paracetamol
- clofibric acid
- lamotrigine (see below)
- morphine
- salicylic acid
- temazepam

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

Contraindicated co-administration

EVRA should not be co-administered with drug combinations containing paritaprevir/ritonavir, ombitasvir, and/or dasabuvir due to potential for ALT elevations.

Healthcare providers are advised to consult the package inserts of concurrently-used medicines to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations and the possible need to adjust dosages.

Laboratory Tests

Certain endocrine and liver function tests and blood components may be affected by EVRA**:**

a) Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin III, decreased protein S, increased noradrenaline-induced platelet aggregability.

b) 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.

c) Other binding proteins may be elevated in serum.

d) 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 either decrease or remain unchanged.

e) 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.

f) Glucose tolerance may be decreased.

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

4.6 Fertility, pregnancy and lactation

EVRA is contraindicated for use in pregnancy.

A small amount of combination hormonal contraceptive steroids have been identified in the milk of breastfeeding mothers and [~~a few~~] adverse effects on the child have been reported, including jaundice and breast enlargement.

In addition, EVRA given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. The breastfeeding mother should be advised not to use EVRA but to use other forms of contraception until she 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

SIDE EFFECTS

Clinical trial data

The safety of EVRA was evaluated in 3 330 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 medication and provided safety data.

The most common side effects reported during clinical trials were breast symptoms, headache, application site disorder and nausea. The most common events leading to discontinuation were application site reaction, breast symptoms (including breast discomfort, breast engorgement and female breast pain), nausea, headache and emotional lability.

Side effects reported by ≥ 1 % of EVRA-treated subjects in these trials are shown in Table 1.

Table 1. Side effects Reported by ≥ 1 % of EVRA-treated Subjects in Three Phase III Clinical Trials

System/Organ Class Adverse reaction	**EVRA** **(n=3 322)** **%**
Investigations	
Weight increased	2,7 %
Nervous system disorders	
Headache	21,0 %
Dizziness	3,3 %
Migraine	2,7 %
Gastrointestinal disorders	
Nausea	16,6 %
Abdominal pain	8,1 %
Vomiting	5,1 %
Diarrhoea	4,2 %

Abdominal distension	1,7 %
Skin and subcutaneous tissue disorders	
Acne	2,9 %
Pruritus	2,5 %
Skin irritation	1,1 %
Musculoskeletal and connective tissue disorders	
Muscle spasms	2,1 %
Infections and infestations	
Vaginal yeast infection	3,9 %
General disorders and administration site conditions	
Application site disorder	17,1 %
Fatigue	2,6 %
Malaise	1,1 %
Reproductive system and breast disorders	
Breast symptoms	22,4 %
Dysmenorrhoea	7,8 %
Vaginal bleeding and menstrual disorders	6,4 %
Uterine spasm	1,9 %

Vaginal discharge	1,9 %
Psychiatric disorders Mood, affect and anxiety disorders	 6,3 %

Additional side effects that occurred in < 1 % of EVRA-treated subjects in the above clinical trial dataset are listed in Table 2.

Table 2. Side Effects Reported by < 1 % of EVRA-treated Subjects in Three Phase III Clinical Trials
System/Organ Class Adverse reaction
Investigations Increased blood pressure, lipid disorders
Respiratory, thoracic and mediastinal disorders Pulmonary embolism
Skin and subcutaneous tissue disorders Chloasma, contact dermatitis, erythema
General disorders and administration site conditions Fluid retention
Hepatobiliary disorders Cholecystitis
Reproductive system and breast disorders

Galactorrhoea, genital discharge, premenstrual syndrome, vulvovaginal dryness
Psychiatric disorders Insomnia, decreased libido, increased libido

Postmarketing Data

Additional side effects first identified during postmarketing experience with EVRA are listed below.

Investigations

Abnormal blood cholesterol, abnormal blood glucose, decreased blood glucose, increased low density lipoprotein

Cardiac disorders

Acute myocardial infarction, myocardial infarction

Nervous system disorders

Cerebrovascular accidents, cerebral haemorrhage, dysgeusia, intracranial haemorrhage, haemorrhagic stroke, migraine with aura, subarachnoid haemorrhage

Eye disorders

Contact lens intolerance

Respiratory, thoracic and mediastinal disorders

Pulmonary thrombosis

Gastrointestinal disorders

Colitis

Skin and subcutaneous tissues disorders

Alopecia, angioedema, allergic dermatitis, eczema, erythema multiforme, erythema nodosum, exfoliative rash, photosensitivity reaction, generalised pruritus, rash, erythematous rash, pruritic rash, seborrhoeic dermatitis, urticaria.

Metabolism and nutrition disorders

Increased appetite, hyperglycaemia, insulin resistance

Infections and infestations

Pustular rash

Injury, poisoning and procedural complications

Contact lens complication

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

Vascular disorders

Arterial thrombosis, hypertension, hypertensive crisis, thrombosis, venous thrombosis

General disorders and administration site conditions

Administration site reactions, face oedema, irritability, localised oedema, peripheral oedema, pitting oedema

Immune system disorders

Anaphylactic reaction, hypersensitivity

Hepatobiliary disorders

Cholelithiasis, cholestasis, hepatic lesion, cholestatic jaundice

Reproductive system and breast disorders

Amenorrhoea, breast mass, cervical dysplasia, hypomenorrhoea, metrorrhagia, oligomenorrhoea, suppressed lactation

Psychiatric disorders

Anger, emotional disorder, irritability

The following side effects have been reported with the post-marketing use of hormonal contraceptives: severe depression with a higher risk of suicidal thoughts/behavior and suicide.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via “6.04 Adverse Drug Reaction Reporting Form” found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/index/8

Alternatively, suspected adverse reactions may be reported directly to Acino Pharma (Pty) Ltd:
E-mail: drugsafety_ZA@acino.swiss Tel: 060 998 7896

4.9 Overdose

Overdosage may cause nausea and vomiting. Vaginal bleeding may occur in females. In case of suspected overdose, all transdermal contraceptive systems should be removed and symptomatic treatment given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 18.7 Contraceptive preparations (transdermal patch)

Mechanism of action

EVRA acts through the mechanism of gonadotropin suppression by the oestrogenic and progestational actions of ethinyloestradiol and norelgestromin. The primary mechanism of action is inhibition of ovulation.

Receptor and sex hormone-binding globulin (SHBG) binding studies, as well as studies in animals and humans, have shown that both norgestimate (NGM) and norelgestromin, the major serum metabolite of norgestimate following oral administration, exhibit high progestational activity with minimal intrinsic androgenicity.

Transdermally-administered norelgestromin, in combination with ethinyloestradiol, does not counteract the oestrogen-induced increases in SHBG, resulting in lower levels of free testosterone in serum compared to baseline.

5.2 Pharmacokinetic properties

Absorption

Following application of a single patch of EVRA**,** both norelgestromin and EE appear in the serum, reach a plateau by approximately 48 hours, and are maintained at an approximate steady state for 7 days. Steady state concentrations C_{SS} for norelgestromin and EE during one week of patch wear are approximately 0,8 ng/mℓ and 50 pg/mℓ, respectively, and are generally consistent from all application sites.

Conditions of cold, heat, humidity and exercise did not affect the transdermal absorption and pharmacokinetics of norelgestromin and EE.

Results from an EVRA study of extended wear of a single contraceptive patch for 7 days and 10 days indicated that target steady state concentrations C_{SS} of norelgestromin and EE were maintained during a 3-day period of extended wear of EVRA (10 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. Ethinyloestradiol is extensively bound to serum albumin.

Biotransformation

Since EVRA is applied transdermally, first-pass metabolism (via the gastro-intestinal tract and/or liver) of norelgestromin and EE is avoided. Hepatic metabolism of norelgestromin occurs and

metabolites include norgestrel, which is largely bound to SHBG, and various hydroxylated and conjugated metabolites.

Ethinyloestradiol is also metabolised to various hydroxylated products and their glucuronide and sulfate conjugates.

Elimination

Following removal of patches, the elimination kinetics of norelgestromin and EE were consistent for all studies with half-life values of approximately 28 hours and 17 hours, respectively. The metabolites of norelgestromin and EE 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 pharmacokinetic (PK) parameters.

In a study comparing EVRA to an oral contraceptive containing norgestimate (parent component of norelgestromin) 250 μg/ethinyloestradiol 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.

Norelgestromin and EE demonstrate linear kinetics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The Active ingredients are norelgestromin (NGMN) and ethinyloestradiol (EE).

The other inactive ingredients are polyisobutylene, polybutene, crospovidone, non-woven polyester fabric and lauryl lactate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

24 Months

6.4 Special precautions for storage

Store at or below 30° C.

Do not refrigerate or freeze.

Store patches in their protective sachets inside the original container.

Keep out of reach of children.

6.5 Nature and contents of the container

Each container has 3, 9 or 18 EVRA transdermal patches in individual foil-lined sachets.

A 20 cm^2 transdermal patch with radius corners consisting of

i. a beige flexible backing

ii. colourless adhesive containing the active components and

iii. a clear, peel-cut release liner

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

Midrand,

1686

8 REGISTRATION NUMBER

36/18.7/0491

9 DATE OF FIRST AUTHORISATION

Date on the registration certificate: 12 November 2004

10 DATE OF REVISION OF THE TEXT

23 May 2022