เอกสารกำกับยาสำหรับแพทย์ฉบับภาษาอังกฤษ

EVRA®

PRODUCT NAME

EVRA®
Norelgestromin / Ethinyl estradiol

DOSAGE FORMS AND STRENGTHS

EVRA is a thin, matrix-type transdermal patch consisting of three layers:
The backing layer is composed of a beige flexible film consisting of a low-density pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive layer from the environment.

The middle layer contains polyisobutylene/polybutene adhesive, crospovidone, non-woven polyester fabric and lauryl lactate as inactive components. The active components in this layer are the hormones, norelgestromin (NGMN) and ethinyl estradiol (EE).

The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a polydimethylsiloxane coating on the side that is in contact with the middle adhesive layer.

EVRA (manufactured by LTS Lohmann Therapie-Systeme AG) is a transdermal patch containing 6 mg NGMN and 600 micrograms EE.
Each EVRA transdermal patch has a contact surface area of 20 cm^2 and is designed to provide continuous delivery of NGMN and EE into the bloodstream over a seven-day duration of wear. (see *Pharmacokinetic Properties*.)

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

Female Contraception

Dosage and 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.

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.

Dosage

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

Only one patch is to 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, 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 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 the 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 coital exposure has occurred during such an extended patch-free interval, the possibility of fertilization should be considered.

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.

If the EVRA patch lifts at the edges or completely detaches and remains detached, insufficient drug delivery occurs.
If EVRA remains even partly detached:

- **for less than one day** (up to 24 hours): it should be reapplied 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 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.

A patch should not be reapplied 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 reattached, 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 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 coital exposure has occurred during such an extended patch-free interval, the possibility of fertilization 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". 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

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.

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 must 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 a physician before initiating treatment with EVRA. If coital exposure has occurred during such an extended patch-free interval, the possibility of fertilization 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 *Pregnancy and Breast feeding* and *Warnings and Precautions* – Thromboembolic and *other vascular disorders*.)

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 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, a cause other than EVRA should be considered.

The incidence of breakthrough bleeding and spotting with EVRA is statistically and clinically comparable to that seen with oral contraceptives containing 20 – 40 mcg of EE.
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.

In case of vomiting or diarrhea

Unlike oral contraceptives, dose delivery by transdermal application should be unaffected by vomiting or diarrhea.

In case of 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.

Adhesion of EVRA patch

Patch adhesion was assessed indirectly by replacement rates for complete and partial patch detachment. Experience with more than 70000 EVRA patches worn for contraception for 6-13 cycles showed that 4.7% of patches were replaced because they either fell off (1.8%) or were partly detached (2.9%). Similarly, in a small study of patch wear under conditions of physical exertion and variable temperature and humidity, less than 2% of patches were replaced for complete or partial detachment.

Special populations

Pediatrics

Safety and efficacy of EVRA was established in women from 18 years of age. Safety and efficacy are expected to be the same for post-pubertal 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 as there is a suggestion in the literature that the unbound fraction of EE is higher, EVRA should be used with supervision in this population.

Hepatic impairment

EVRA is contraindicated in this population.

Administration

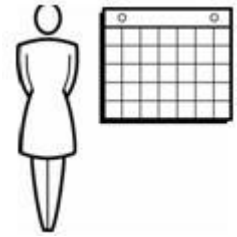
To achieve maximum contraceptive effectiveness, EVRA must be used exactly as directed. Complete instructions to facilitate patient counseling on proper system usage may be found in the Detailed Patient Labeling.

Transdermal contraceptive system overview

This system uses a 28-day, four-week cycle. A new patch is applied each week for three weeks – 21 total days. Week Four is patch-free. Withdrawal bleeding is expected during this time.
This means that every new patch will be applied on the same day of the week. This day is known as the "Patch Change Day". For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only 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.

On the day after Week Four ends a new four-week cycle is started by applying a new patch. Under no circumstances should there be more than a 7-day patch-free interval between dosing cycles.

Clinical trials demonstrated that subjects randomized to EVRA were able to adhere to the weekly dosing regimen better than with daily dosing of oral contraceptives. (see *PHARMACOLOGICAL PROPERTIES – Clinical studies*.)

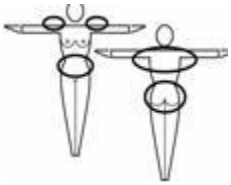


If the patient is starting EVRA for the **first time,** she should **wait until the day she begins her menstrual period.** Either a First Day start or Sunday start may be utilized (see below). The day she applies her first patch will be Day 1. Her "Patch Change Day" will be on this day every week.

First Day Start: the patient should apply her first patch during the first 24 hours of her period. If therapy starts after Day 1 of the menstrual cycle, a non-hormonal contraceptive (such as a condom or diaphragm) should be used concurrently for the first 7 consecutive days of the first treatment cycle.

OR

Sunday Start: the patient should apply her first patch on the first Sunday after her period starts. She must use back-up contraception for the first week of her first cycle only. If the menstrual period begins on a Sunday, the first patch should be applied on that day. No back-up contraception is needed.

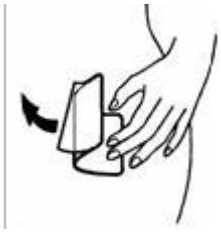


Where to apply the patch. The patch should be applied to clean, dry, intact healthy skin on the buttock, abdomen, upper outer arm or upper torso, in a place where it won't be rubbed by tight clothing. EVRA should not be placed on skin that is red, irritated or cut, nor should it be placed on the breasts.

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.

Application of the EVRA patch

The foil pouch is opened by tearing it along the edge using the fingers. A corner of the patch is grasped firmly and gently removed from the foil pouch. Sometimes patches can stick to the inside of the pouch – the patient should be careful not to accidentally remove the clear liner as she removes the patch. Then half of the clear protective liner is peeled away. The patient should avoid touching the sticky surface of the patch.

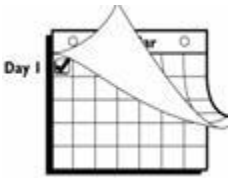


The patch is positioned on the skin and the other half of the liner is removed. The patient should press down firmly on the patch with the palm of her hand for 10 seconds, making sure that the edges stick well. She should check her patch every day to make sure it is sticking.

The patch is worn for 7 days (one week). On the "Patch Change Day", Day 8, the used patch is removed and a new one is applied immediately. The used patch still contains some active hormones – it should be thrown away by carefully folding it in half so that it sticks to itself.

A new patch is applied on Week Two (Day 8) and again on Week Three (Day 15), on the usual "Patch Change Day". Patch changes may occur at any time on the Change Day. Consecutive EVRA patches should be applied to a new spot on the skin to help avoid potential irritation, although they may be kept within the same anatomic site.

Week Four is patch-free (Day 22 through Day 28), thus completing the four-week contraceptive cycle. Bleeding is expected during this time.



The next four-week cycle is started by applying a new patch on the usual "Patch Change Day", the day after Day 28, no matter when the menstrual period begins or ends.

Under no circumstances should there be more than a 7-day patch free interval between dosing cycles.

Patch adhesion was assessed indirectly by replacement rates for complete and partial patch detachment. Experience with more than 70000 EVRA patches worn for contraception for 6-13 cycles showed that 4.7% of patches were replaced because they either fell off (1.8%) or were partly detached (2.9%). Similarly, in a small study of patch wear under conditions of physical exertion and variable temperature and humidity, less than 2% of patches were replaced for complete or partial detachment.

If the EVRA patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs.

If the patch remains even partly detached:

- **for less than one day** (up to 24 hours), the patient should try to reapply it to the same place or replace it with a new patch immediately. No back-up contraception is needed. The woman's "Patch Change Day" will remain the same.
- **for more than one day (24 hours or more) OR if the patient is not sure how long the patch has been detached**, SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new cycle immediately by putting on a new patch. There is now a new "Day 1" and a new "Patch Change Day." Back-up contraception must be used for the first week of the new cycle only.

A patch should not be reapplied 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 reapplied, a new patch should be applied immediately. Supplemental adhesives or wraps should not be used to hold the EVRA patch in place.

If the patient forgets to change her patch…

- **at the start of any patch cycle** (Week One/Day 1): SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should apply the first patch of her new cycle as soon as she remembers. There is now a new "Patch Change Day" and a new "Day 1". The patient must use back-up contraception for the first week of her new cycle.
- **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), she should apply a new patch immediately. The next patch should be applied on the usual "Patch Change Day". No back-up contraception is needed.
- for **more than two days** (48 hours or more), SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new four-week cycle immediately by putting on a new patch. There is now a new "Patch Change Day" and a new "Day 1". The patient must use back-up contraception for one week.

- **at the end of the patch cycle (Week Four/Day 22), Week** Four (Day 22): If the patient forgets to remove her patch, she should take it off as soon as she remembers. The next cycle should be started on the usual "Patch Change Day", which is the day after Day 28. No back-up contraception is needed.

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 PATIENT MAY NOT BE PROTECTED FROM PREGNANCY and back-up contraception must 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 fertilization should be considered.

Change Day Adjustment

If the patient wishes to move her Patch Change Day she should complete her current cycle, removing the third EVRA patch on the correct day. During the patch-free week, a new Patch Change Day may be selected by applying a new EVRA patch 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 physician before initiating treatment with EVRA.

Use after Childbirth

Women who elect not to breastfeed should start contraceptive therapy with EVRA no sooner than 4 weeks after childbirth. (see *Warnings and Precautions - Thromboembolic and other vascular disorders* and *Pregnancy and Breast-feeding.*)

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, a cause other than EVRA should be considered.

Two adequate and well-controlled trials demonstrated that the incidence of breakthrough bleeding and spotting with EVRA is statistically and clinically comparable to that seen with ORTHO-CYCLEN® and TRIPHASIL®.

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.

In Case of Vomiting or Diarrhea

Unlike oral contraceptives, dose delivery by transdermal application should be unaffected by vomiting. Dose delivery is also expected to be unaffected by diarrhea.

In Case of 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.

Additional instructions for dosing

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing hormonal contraceptives. In cases of breakthrough bleeding, structural abnormalities and dysfunctional uterine bleeding should be considered as potential causes. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to a hormonal contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Use of hormonal contraceptives in the event of a missed menstrual period:

1. If the woman has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Hormonal contraceptive use should be discontinued and a non-hormonal method should be used until pregnancy is ruled out.
2. If the woman has adhered to the prescribed regimen and misses one period, she should continue using her contraceptive patches.
3. If the woman has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing hormonal contraceptive use.

Contraindications

EVRA should not be used in women who currently have the following conditions:

- Thrombophlebitis, thromboembolic disorders

- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Known thrombophilic conditions
- Cerebrovascular or coronary artery disease
- Valvular heart disease with complications
- Persistent blood pressure values of ≥ 160 mm Hg systolic or ≥ 100 mm Hg diastolic
- Diabetes with vascular involvement
- Migraine with focal aura
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use
- Acute or chronic hepatocellular disease with abnormal liver function
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy
- Hypersensitivity to any component of this product
- Patients receiving drug combinations with paritaprevir/ritonavir, ombitasvir, and/or dasabuvir due to potential for ALT elevations.

Warnings and Precautions

Smoking and age

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

Body weight ≥ 90 kg

Analyses of phase III data suggest that EVRA may be less effective in users with body weight ≥ 90 kg than in users with lower body weights. Below 90 kg there was no association between body weight and pregnancy. (see *PHARMACOLOGICAL PROPERTIES - Clinical Studies*.)

General

In case of undiagnosed, persistent or recurrent abnormal 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 physician 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 complications, e.g., prolonged immobilization or major surgery, leg surgery or a leg cast, obesity, or family history of thromboembolic disease

- Risk factors for arterial disease, e.g., smoking, hyperlipidemia, 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
- Family history of cholestatic jaundice (e.g., Rotor, Dubin-Johnson Syndrome)

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 hospitalization. The risk of thromboembolic disease associated with hormonal contraceptives returns to baseline after the combined hormonal contraceptive (CHC) 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 CHC is re-started after ≥4 weeks of discontinuation is at least as high as the risk of VTE when a CHC is initially started.

Epidemiologic, case-control studies were conducted in the U.S. using healthcare claims data to evaluate the risk of VTE among women aged 15–44 who used ORTHO EVRA® (a transdermal patch bioequivalent to EVRA) compared to women who used oral contraceptives containing 30-35 mcg of ethinyl estradiol (EE) and either norgestimate (NGM) or levonorgestrel (LNG). NGM is the prodrug for norelgestromin, the progestin in ORTHO EVRA®. These studies (see Table 1) used slightly different designs and reported odds ratios ranging from 0.9 (indicating no increase in risk) to 2.5 (indicating an approximate doubling of risk). One study (i3 Ingenix) included patient chart review to confirm the VTE occurrence. Two studies using different databases were conducted by the Boston Collaborative Drug Surveillance Program (BCDSP) with LNG-containing oral contraceptives as the comparator.

Table 1: Estimates (Odds Ratios) of Venous Thromboembolism Risk in Current Users of ORTHO EVRA® Compared to Oral Contraceptive Users		
Epidemiologic Study	**Comparator Product**	**Odds Ratio (95% C.I.)**
i3 Ingenix NGM	NGM/35 mcg EE[A]	Data set one: 2.5 (1.1–5.5)[B]
		Data set two: 1.4 (0.5–3.7)[C]
		Cumulative: 2.2 (1.2–4.0)[D]
BCDSP NGM[E]	NGM/35 mcg EE	Data set one: 0.9 (0.5–1.6)[F]
		Data set two: 1.1 (0.6–2.1)[G]
		Data set three: 2.4 (1.2–5.0)[H]
		Cumulative: 1.2 (0.9–1.8)[I]
BCDSP LNG (Database one)	LNG[J]/30 mcg EE	2.0 (0.9–4.1)[K]
BCDSP LNG (Database two)	LNG/30 mcg EE	1.3 (0.8–2.0)[L]

[A] NGM = norgestimate; EE = ethinyl estradiol
[B] Increase in risk of VTE is statistically significant; 33 months of data
[C] Separate estimate from 24 months of data on new cases not included in the previous estimate.
[D] Cumulative odds ratio.
[E] BCDSP = Boston Collaborative Drug Surveillance Program
[F] Initial 36 months of data.
[G] Separate estimate from 17 months of data on new cases not included in the previous estimate.
[H] Separate estimate from 14 months of data on new cases not included in the previous estimates.
[I] Cumulative odds ratio.
[J] LNG = levonorgestrel
[K] 48 months of data.
[L] 69 months of data.

As with any combination hormonal contraceptive, the clinician should be alert to the earliest manifestations of thromboembolic disorders (thrombophlebitis, VTE including pulmonary embolism, cerebrovascular disorders, and retinal thrombosis). 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 immobilization. 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 thromboses (e.g., stroke, myocardial infarction) is increased by the presence of other predisposing factors such as cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia and increasing age. Hormonal contraceptives have been associated with these serious vascular complications. The risk of vascular disease may be less severe with hormonal contraceptive formulations containing lower dosages of estrogen and progestogen, although this has not been conclusively established.

The risk of serious cardiovascular side effects increases with age and with heavy smoking and is quite marked in smokers over 35 years of age. Users of hormonal contraceptives should be strongly advised not to smoke.

Due to the vague symptomatology of many thromboembolic events, hormonal contraceptives 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 hormonal contraceptives. Hormonal contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema 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 hormonal contraceptives. Studies indicate that this increase is more likely to occur in older hormonal contraceptive users and with extended duration of use. For many users, elevated blood pressure will return to normal after they stop taking hormonal contraceptives. There is no difference in the occurrence of hypertension between former and never users. In three contraception trials of EVRA (n=1530, n=819, and n=748, respectively) mean changes from baseline in systolic and diastolic blood pressure were less than 1 mm mercury.

Users with hypertension should have their condition under control before hormonal contraceptive therapy can be started. Hormonal contraceptive therapy should be discontinued if significant persistent elevation of blood pressure (≥ 160 mm Hg systolic or ≥ 100 mm 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 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/100000 for users, a risk that increases after 4 or more years of use, especially with hormonal contraceptives containing 50 micrograms or more of estrogen. Rupture of benign hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown that combination hormonal contraceptive users have an increased risk of developing hepatocellular carcinoma.

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

Carcinoma of the reproductive organs and breasts

Most studies suggest that use of hormonal contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk has been reported to be related to duration of use, before the first term pregnancy.

A meta-analysis of 54 epidemiological studies reports that users who are currently using combined hormonal contraceptives or have used them in the past 10 years are at a slightly increased risk of having breast cancer diagnosed, although the additional cancers tend to be localized to the breast. It is not possible to infer from these data whether the patterns of risk observed are due to an earlier diagnosis of breast cancer in ever-users, the biological effects of hormonal contraceptives, or a combination of both factors. This meta-analysis also suggests that the age at which users discontinue the use of combined hormonal contraceptives is an important risk factor for breast cancer; the older the age at stopping, the more breast cancers are diagnosed. Duration of use was considered less important.

The possible increase in risk of breast cancer should be discussed with users and weighed against the benefits of combined hormonal contraceptives, taking into account the evidence that they offer substantial protection against the risk of developing ovarian and endometrial cancer.

Some studies suggest that hormonal contraceptive use has been associated with an increased risk of cervical intraepithelial neoplasia in some populations of users. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

Metabolic effects

Hormonal contraceptives may cause a decrease in glucose tolerance. This effect has been shown to be directly related to estrogen 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.

A small proportion of women will have persistent hypertrigylceridemia while taking hormonal contraceptives. Changes in serum triglycerides and lipoprotein levels have been reported in hormonal contraceptive users.

Headache

As with all hormonal contraceptives, 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 amenorrhea may be encountered in users on hormonal contraceptives, 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 amenorrhea or oligomenorrhea after discontinuing hormonal contraception, especially when such a condition was pre-existent.

Chloasma

Chloasma may occasionally occur with 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.

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. In general, transdermal patches are 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 the patch 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 *Pharmacokinetic Properties - Transdermal versus Oral Contraceptives*.)

Interactions

Changes in contraceptive effectiveness associated with coadministration of other drugs

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

- some anti-epileptics (e.g. carbamazepine, eslicarbazepine 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)
- 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 metabolizing 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 coadministered drugs

Some drugs and grapefruit juice may increase the plasma levels of ethinyl estradiol if coadministered. Examples include:

- acetaminophen
- 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 coadministered drugs

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

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

- cyclosporine
- omeprazole
- prednisolone
- selegiline
- theophylline
- tizanidine

- voriconazole

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

- acetaminophen
- clofibric acid
- lamotrigine (see below)
- morphine
- salicyclic acid
- temazepam

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

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.

Physicians are advised to consult the labeling of concurrently-used drugs 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 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.

Pregnancy and Breast-feeding

Pregnancy

EVRA is contraindicated for use in 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, particularly insofar as cardiac anomalies and limb reduction defects are concerned, when hormonal contraceptives are used inadvertently during early pregnancy.

Breast-feeding

A small amount of the contraceptive steroids and/or their metabolites may be excreted with the milk. Small amounts of combination hormonal contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination hormonal contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use EVRA or other combination hormonal contraceptives but to use other forms of contraception until the child is fully weaned.

Effects on Ability to Drive and Use Machines

None known.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of norelgestromin/ethinyl estradiol based on the comprehensive assessment of the available adverse event information. A causal relationship with norelgestromin/ethinyl estradiol cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of ORTHO EVRA®/EVRA was evaluated in 3330 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 (ORTHO EVRA® or oral contraceptive comparator), took at least one dose of study medication and provided safety data.
The most common adverse reactions 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.

Adverse reactions reported by ≥ 1% of ORTHO EVRA®-treated subjects in these trials are shown in Table 2.

Table 2: Adverse Reactions Reported by ≥ 1% of ORTHO EVRA®-treated Subjects in Three Phase III Clinical Trials1,2

	ORTHO EVRA®	Mercilon[3]	Triphasil[4]
System/Organ Class	(n=3322)	(n=641)	(n=602)
Adverse reaction	%	%	%
Investigations			
Weight increased	2.7%	1.4%	3.0%
Nervous system disorders			
Headache	21.0%	23.7%	22.1%
Dizziness	3.3%	1.6%	4.5%
Migraine	2.7%	3.4%	2.5%
Gastrointestinal disorders			
Nausea	16.6%	5.9%	17.9%
Abdominal pain[5]	8.1%	9.7%	7.1%
Vomiting	5.1%	2.7%	4.3%
Diarrhea	4.2%	4.5%	3.7%
Abdominal distension	1.7%	0.6%	2.7%
Skin and subcutaneous tissue disorders			
Acne	2.9%	3.6%	3.7%
Pruritus	2.5%	0.8%	0.2%
Skin irritation	1.1%	0.2%	0
Musculoskeletal and connective tissue disorders			
Muscle spasms	2.1%	1.1%	2.5%
Infections and infestations			
Vaginal yeast infection[6]	3.9%	3.9%	5.3%
General disorders and administration site conditions			
Application site disorder[7]	17.1%	Not applicable	Not applicable
Fatigue	2.6%	1.6%	3.2%
Malaise	1.1%	0.8%	0.3%
Reproductive system and breast disorders			
Breast symptoms[8]	22.4%	9.0%	6.1%
Dysmenorrhea	7.8%	3.9%	7.3%
Vaginal bleeding and menstrual disorders[9]	6.4%	5.0%	3.7%
Uterine spasm	1.9%	0.5%	2.2%
Vaginal discharge	1.9%	1.9%	0.7%
Psychiatric disorders			
Mood, affect and anxiety disorders[10]	6.3%	5.1%	6.0%

[1] Trials included are NRGEEP-CONT-002, NRGEEP-CONT-003, and NRGEEP-CONT-004 (principal safety analysis group used for integrated safety summary).

[2] Thirteen patients (8 ORTHO EVRA®, 2 Mercilon, and 3 Triphasil) did not have study medication start dates in the database. These 13 patients (8 of whom had at least one adverse event) were excluded as it could not be determined whether their adverse events were treatment-emergent or not.

[3] **Mercilon** for product containing 150 micrograms desogestrel and 20 micrograms EE.

[4] **Triphasil** for product containing 50 micrograms levonorgestrel and 30 micrograms EE (Days 1-6), 75 micrograms levonorgestrel and 40 micrograms EE (Days 7-11) and 125 micrograms levonorgestrel and 30 micrograms EE (Days 12-21).

[5] The bundled term abdominal pain consists of the preferred terms abdominal pain, abdominal pain upper, and abdominal pain lower.

[6] The bundled term vaginal yeast infection consists of the preferred terms fungal infection (vaginal only), vaginal candidiasis, and vulvovaginal mycotic infection.

[7] The bundled term application site disorder consists of the preferred terms application site dermatitis, application site discoloration, application site erythema, application site hypersensitivity, application site irritation, application site edema, application site pain, application site papules, application site pruritus, application site rash, application site reaction, application site urticaria, and application site vesicles.

[8] The bundled term breast symptoms consists of the preferred terms breast discomfort, breast disorder, breast engorgement, breast enlargement, breast pain, breast swelling, breast tenderness, and fibrocystic breast disease.

[9] The bundled term vaginal bleeding and menstrual disorders consists of the preferred terms menorrhagia, menstrual disorder, menstruation irregular, metrorrhagia, polymenorrhea, and vaginal hemorrhage.

[10] The bundled term mood, affect, and anxiety disorders consists of the preferred terms affect lability, aggression, anxiety, crying, depression, mood altered, mood swings, and tearfulness.

Additional adverse reactions that occurred in < 1% of ORTHO EVRA®-treated subjects in the above clinical trial dataset are listed in Table 3.

Table 3: Adverse Reactions Reported by < 1% of ORTHO EVRA®**-treated Subjects in Three Phase III Clinical Trials[11,12]**

System/Organ Class
Adverse reaction
Investigations
Blood pressure increased, Lipid disorders[13]
Respiratory, thoracic and mediastinal disorders
Pulmonary embolism
Skin and subcutaneous tissue disorders
Chloasma, Dermatitis contact, Erythema
General disorders and administration site conditions
Fluid retention[14]
Hepatobiliary disorders
Cholecystitis
Reproductive system and breast disorders
Galactorrhea, Genital discharge, Premenstrual syndrome, Vulvovaginal dryness
Psychiatric disorders
Insomnia, Libido decreased, Libido increased

[11] Trials included are NRGEEP-CONT-002, NRGEEP-CONT-003, and NRGEEP-CONT-004 (principal safety analysis group used for integrated safety summary).

[12] Thirteen patients (8 ORTHO EVRA®, 2 Mercilon, and 3 Triphasil) did not have study medication start dates in the database. These 13 patients (8 of whom had at least one adverse event) were excluded as it could not be determined whether their adverse events were treatment-emergent or not.

[13] The bundled term lipid disorders consists of the preferred terms blood cholesterol increased, blood triglycerides increased, and hypercholesterolemia.

[14] The bundled term fluid retention consists of the preferred terms fluid retention, generalized edema, and swelling. The bundled term "Fluid retention" is included under the SOC General disorders and administration site conditions because two of the three terms (generalized edema and swelling) occur in that SOC; the preferred term fluid retention occurs in the Metabolism and nutrition disorders SOC.

Postmarketing data

Additional adverse reactions first identified during postmarketing experience with ORTHO EVRA®/EVRA are included in Table 4, the frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports

In Table 4, adverse reactions are presented by frequency category based on spontaneous reporting rates

Table 4: Adverse Reactions Identified During Postmarketing Experience with ORTHO EVRA®/**EVRA by Frequency Category Estimated from Spontaneous Reporting Rates**

Investigations	
Very rare	Blood cholesterol abnormal, Blood glucose abnormal, Blood glucose decreased, Low density lipoprotein increased
Cardiac disorders	
Very rare	Acute myocardial infarction, Myocardial infarction
Nervous system disorders	
Very rare	Cerebral hemorrhage, Cerebrovascular accidents[15], Dysgeusia, Hemorrhage intracranial, Hemorrhagic stroke, Migraine with aura, Subarachnoid hemorrhage
Eye disorders	
Very rare	Contact lens intolerance
Respiratory, thoracic and mediastinal disorders	
Very rare	Pulmonary thrombosis[16]
Gastrointestinal disorders	
Very rare	Colitis
Skin and subcutaneous tissues disorders	
Very rare	Alopecia, Angioedema, Dermatitis allergic, Eczema, Erythema multiforme, Erythema nodosum, Exfoliative rash, Photosensitivity reaction, Pruritus generalized, Rash, Rash erythematous, Rash pruritic, Seborrheic dermatitis, Skin reaction, Urticaria
Metabolism and nutrition disorders	
Very rare	Hyperglycemia, Increased appetite, Insulin resistance
Infections and infestations	
Very rare	Rash pustular
Injury, poisoning and procedural complications	
Very rare	Contact lens complication
Neoplasms benign, malignant and unspecified (Incl cysts and polyps)	
Very rare	Breast cancer, Breast cancer stage IV, Cervix carcinoma, Fibroadenoma of breast, Hepatic adenoma, Hepatic neoplasm, Uterine leiomyoma
Vascular disorders	
Very rare	Arterial thrombosis[17], Hypertension, Hypertensive crisis, Thrombosis[18], Venous thrombosis[19]
General disorders and administration site conditions	
Rare	Administration site reactions[20]
Very rare	Face edema, Irritability, Localized edema, edema peripheral, Pitting edema
Immune system disorders	
Very rare	Hypersensitivity
Hepatobiliary disorders	
Very rare	Cholelithiasis, Cholestasis, Hepatic lesion, Jaundice cholestatic
Reproductive system and breast disorders	
Rare	Amenorrhea
Very rare	Breast mass, Cervical dysplasia, Hypomenorrhea, Menometrorrhagia, Oligomenorrhea, Suppressed lactation

Psychiatric disorders	
Very rare	Anger, Emotional disorder, Frustration

[15] The bundled term cerebrovascular accidents consists of the preferred terms cerebrovascular accident, transient ischemic attack, intracranial venous sinus thrombosis, cerebral infarction, cerebral thrombosis, cerebral venous thrombosis, ischemic cerebral infarction, superior sagittal sinus thrombosis, ischemic stroke, transverse sinus thrombosis, thrombotic stroke, thromboembolic stroke, basilar artery thrombosis, brain stem infarction, carotid artery occlusion, cerebral artery embolism, cerebral artery occlusion, cerebral artery thrombosis, lacunar infarction, and embolic stroke.

[16] The bundled term pulmonary thrombosis consists of the preferred terms pulmonary thrombosis and pulmonary artery thrombosis.

[17] The bundled term arterial thrombosis consists of the preferred terms arterial thrombosis, arterial thrombosis limb, coronary artery thrombosis, iliac artery thrombosis, intracardiac thrombus, and retinal artery occlusion.

[18] The bundled term thrombosis consists of the preferred terms thrombosis, retinal vascular thrombosis, embolism, Budd-Chiari syndrome, renal embolism, and peripheral embolism.

[19] The bundled term venous thrombosis consists of the preferred terms retinal vein occlusion, deep vein thrombosis, venous thrombosis, pelvic venous thrombosis, thrombophlebitis, venous thrombosis limb, jugular vein thrombosis, axillary vein thrombosis, superficial thrombophlebitis, portal vein thrombosis, mesenteric vein thrombosis, vena cava thrombosis, renal vein thrombosis, splenic vein thrombosis, and hepatic vein thrombosis.

[20] The bundled term administration site reactions consists of the preferred terms application site burn, application site dryness, application site scar, application site bruising, application site photosensitivity reaction, application site exfoliation, application site swelling, application site scab, application site paresthesia, application site warmth, application site bleeding, application site inflammation, application site pustules (moved from Infections and infestations SOC), application site induration, application site atrophy, application site excoriation, application site discomfort, application site anesthesia, application site infection, application site ulcer, application site eczema, application site nodule, application site discharge, application site abscess, application site mass, application site erosion and application site odor.

Overdose

Symptoms and signs

Overdosage may cause nausea and vomiting. Vaginal bleeding may occur in females.

Treatment

In case of suspected overdose, all transdermal contraceptive systems should be removed and symptomatic treatment given.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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

Mechanism of action

EVRA acts through the mechanism of gonadotropin suppression by the estrogenic and progestational actions of ethinyl estradiol (EE) and norelgestromin (NGMN). The primary

mechanism of action is inhibition of ovulation, but alterations to the cervical mucus, the fallopian tube motility and to the endometrium may also contribute to the efficacy of the product.

Receptor and sex hormone binding globulin (SHBG) binding studies, as well as studies in animals and humans, have shown that both norgestimate (NGM) and NGMN, the major serum metabolite of NGM following oral administration, exhibit high progestational activity with minimal intrinsic androgenicity, which illustrates the selective action of EVRA. Transdermally-administered norelgestromin in combination with EE does not counteract the estrogen-induced increases in SHBG, resulting in lower levels of free testosterone in serum compared to baseline.

The following non-contraceptive health benefits related to the use of combination hormonal contraceptives are supported by epidemiological studies which largely utilized hormonal contraceptive formulations containing estrogen at doses exceeding 35 micrograms of EE or 50 micrograms of mestranol.

Effects on menses:

- increased menstrual cycle regularity
- decreased blood loss and decreased incidence of iron deficiency anemia
- decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation:

- decreased incidence of functional ovarian cysts
- decreased incidence of ectopic pregnancies

Other effects:

- decreased incidence of fibroadenomas and fibrocystic disease of the breast
- decreased incidence of acute pelvic inflammatory disease
- decreased incidence of endometrial cancer
- decreased incidence of ovarian cancer

Pharmacodynamic effects

Clinical studies

Three contraceptive trials involving 4578 women for 31026 cycles were conducted worldwide. In these trials, 3319 women received EVRA and 1248 women received one of two oral contraceptives, one containing levonorgestrel/EE or one containing desogestrel/EE. The results of these trials showed that the efficacy of EVRA was similar to that of the oral contraceptives.

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 a baseline body weight ≥ 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 - Effects on age, body weight, and body surface area*), the greater proportion of pregnancies among women at or above 90 kg was statistically significant and suggests that EVRA may be less effective in these women.

A multi-centre dose selection study for EVRA showed that EVRA inhibited ovulation to the same extent as the oral contraceptive comparator. The bleeding profile of EVRA in this study was similar to that of the oral contraceptive at all cycles. In addition, user compliance with EVRA dosing was significantly better than that seen with the oral contraceptive.
Among more than 3000 women who used EVRA for up to 13 cycles, the mean change in body weight from baseline to the end of treatment was an increase of 0.3 kg. In a 9-cycle placebo-controlled trial there was no difference between EVRA and placebo in the mean change in body weight from baseline to the end of treatment.

Pharmacokinetic studies with EVRA demonstrated consistent elimination kinetics for NGMN and EE with half-life of approximately 28 hours and 17 hours, respectively. One clinical trial assessed the return of hypothalamic-pituitary-ovarian axis function post-therapy and found that FSH, LH and estradiol mean values, though suppressed during therapy, returned to near baseline values during the 6 weeks post-therapy. Therefore, it is anticipated that following discontinuation of EVRA treatment, return to fertility will be rapid, approximating that seen with oral contraceptives.

Pharmacokinetic Properties

Absorption

Following application of EVRA, both NGMN and EE rapidly appear in the serum, reach a plateau by approximately 48 hours, and are maintained at an approximate steady-state throughout the wear period. C_{ss} concentrations for NGMN 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 studies and application sites.

The absorption of NGMN and EE following application of EVRA to the abdomen, buttock, upper outer arm and upper torso (excluding breast) was evaluated in a cross-over design study. The results of this study indicated that C_{ss} and AUC for the buttock, upper arm and torso for each analyte were equivalent. Strict bio-equivalence requirements for AUC were not met in this study for the abdomen. However, in a separate parallel group multiple application pharmacokinetic study, C_{ss} and AUC for the buttock and abdomen were not statistically different. In a dose-ranging study, EVRA caused effective ovulation suppression when applied to the abdomen. Therefore, all four sites are therapeutically equivalent.
The absorption of NGMN and EE 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 NGMN 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. There was no significant effect of cool water on these parameters.

Results from a study with EVRA of extended wear of a single contraceptive patch for 7 days and 10 days indicated that target C_{ss} of NGMN and EE 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

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

Metabolism

Since EVRA is applied transdermally, first-pass metabolism (via the gastro-intestinal tract and/or liver) of NGMN and EE that would be expected following oral administration is avoided. Hepatic metabolism of NGMN occurs and metabolites include norgestrel, which is largely bound to SHBG, and various hydroxylated and conjugated metabolites. EE is also metabolized to various hydroxylated products and their glucoronide and sulfate conjugates.

Elimination

Following removal of patches, the elimination kinetics of NGMN and EE were consistent for all studies with half-life values of approximately 28 hours and 17 hours, respectively. The metabolites of NGMN and EE are eliminated by renal and fecal pathways.

Linearity/non-linearity

In multiple dose studies, C_{ss} and AUC for NGMN and EE were found to increase slightly over time when compared to Week 1 of Cycle 1. In a three-cycle study, these pharmacokinetic parameters reached steady-state conditions during all three weeks of Cycle 3. These observations are indicative of linear kinetics of NGMN and EE from EVRA use.

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 NGM 250 mcg/EE 35 mcg, C_{max} values were 2-fold higher for NGMN and EE in subjects administered the oral contraceptive compared to EVRA, while overall exposure (AUC and C_{ss}) was comparable in subjects treated with EVRA. Inter-subject variability (%CV) for the PK parameters following delivery from EVRA was higher relative to the variability determined from the oral contraceptive.

In a study comparing ORTHO EVRA (a transdermal patch with a similar PK profile to EVRA) to an oral contraceptive containing NGM 250 mcg/EE 35 mcg, overall exposure for NGMN and EE (AUC and C_{ss}) was higher in subjects treated with ORTHO EVRA for both Cycle 1 and Cycle 2 compared to that for the oral contraceptive, while C_{max} values were higher in subjects administered the oral contraceptive. Under steady-state conditions, AUC_{0-168} and C_{ss} for EE were approximately 55% and 60% higher, respectively, for the transdermal patch, and the C_{max} was about 35% higher for the oral contraceptive. Inter-subject variability (%CV) for the PK parameters following delivery from ORTHO EVRA was higher relative to the variability determined from the oral contraceptive.

In the following table, percent change in concentrations (%CV) of markers of systemic estrogenic activity (Corticosteroid Binding Globulin [CBG], Sex Hormone Binding Globulin [SHBG], and Corticosteroid Binding Globulin Binding Capacity [CBG-BC]) from Cycle 1, Day 1 to Cycle 1, Day 22 are presented. Overall, percent change in CBG and CBG-BC concentrations were similar for EVRA and oral contraceptive users; percent change in SHBG concentrations were higher for EVRA users compared to women taking the oral contraceptive. Within each group, the absolute values for CBG, SHBG, and CBG-BC were similar for Cycle 1, Day 22 and Cycle 2, Day 22.

Table 5: Mean percent Change (%CV) in CBG, SHBG, and CBG-BC Concentrations Following Once-daily Administration of an Oral Contraceptive (containing NGM 250 mcg/EE 35 mcg) for One Cycle and Application of EVRA for One Cycle in Healthy Female Volunteers

Parameter	ORAL CONTRACEPTIVE (% change from Day 1 to Day 22)	ORTHO EVRA® (% change from Day 1 to Day 22)
CBG	157 (33.4)	153 (40.2)
SHBG	200 (43.2)	334 (39.3)
CBG-BC	139 (34.8)	128 (36.3)

Despite the differences in the PK profiles of ORTHO EVRA® and an oral contraceptive (containing NGM 250 mcg/EE 35 mcg), estrogenic activity, as assessed by hepatic globulin synthesis, was similar when evaluating CBG and CBG-BC and higher for ORTHO EVRA® when evaluating SHBG.

The clinical relevance of the difference in PK profile and pharmacodynamic (PD) response between transdermal and oral delivery is not known.

Effects of age, body weight, and body surface area

The effects of age, body weight, body surface area and race on the pharmacokinetics of NGMN and EE were evaluated in 230 healthy women from nine pharmacokinetic studies of single 7-day applications of ORTHO EVRA®.. For both NGMN 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 NGMN and EE following application of ORTHO EVRA® may be associated with any or all of the above demographic parameters. There was no significant effect of race with respect to Caucasians, Hispanics and Blacks.

NON-CLINICAL INFORMATION

Preclinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. Studies conducted to examine the dermal effects of EVRA indicate this system has no potential to produce sensitization and results in only mild irritation when applied to rabbit skin.

PHARMACEUTICAL INFORMATION

List of Excipients

Backing layer:	Low-density pigmented polyethylene outer layer, polyester inner layer
Middle layer:	Polyisobutylene/polybutene adhesive, crospovidone, non-woven polyester fabric and lauryl lactate
Third layer:	Transparent polyethylene terephthalate (PET) film with a polydimethylsiloxane coating

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.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Do not store above 30°C.

Store patches in their protective sachet inside the original box.
Do not store in the refrigerator or freezer.
Keep out of the sight and reach of children.

Nature and Contents of Container

Patches: 3 per box.

Instructions for Use and Handling and Disposal

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. Used patches should not be flushed down the toilet. Keep out of the reach of children.

Manufactured by

LTS Lohmann Therapie-Systeme AG, Andernach, Germany

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Imported by

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Warnings

1. Do not use in patient with thromboembolic disorder and liver disease.
2. Do not use in wen known risk of thromboembolic disorder such as a past history of vasculitis, obesity, diabetes mellitus, hypertension.
3. Do not use in patients with a history of liver tumors and patients or suspected cancer related to sex hormones such as breast cancer or genital cancer.
4. Be caution when use in women who smoke, especially with aged more than 35 years old. Consult physician before use.
5. In case of use other than contraception, please consult the physician.
6. If any undesirable effects occur, please consult the physician immediately.