SCHEDULING STATUS

S4

EVOREL® SEQUI, 50 µg; 50 µg, 170 µg, Patches

Estradiol/norethisterone

EVOREL SEQUI contains no sugar.

Read all of this leaflet carefully before you start using EVOREL SEQUI patches

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- EVOREL SEQUI has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What EVOREL SEQUI is and what it is used for
2. What you need to know before you use EVOREL SEQUI
3. How to use EVOREL SEQUI
4. Possible side effects
5. How to store EVOREL SEQUI
6. Contents of the pack and other information

1. What EVOREL SEQUI is and what it is used for

Each pack of EVOREL SEQUI contains two types of patches:

- EVOREL 50
- EVOREL CONTI

EVOREL 50 patches contain an estrogen called estradiol.

EVOREL CONTI patches contain estradiol and norethisterone.

EVOREL SEQUI is used for hormone replacement therapy (HRT) in the treatment of symptoms of menopause such as hot flushes and vaginal dryness in women who still have a womb.

The EVOREL 50 and the EVOREL CONTI patches replace the natural estrogen that is normally released by the ovaries.

In women who still have a womb, using estrogen without using a progestogen regularly may cause the lining of the womb to build up and thicken, which may lead to cancer of the womb. It is necessary to shed this lining regularly to prevent any problems occurring. Adding a progestogen hormone to the estrogen treatment for approximately 2 weeks of a 4-week cycle will cause the lining to be shed to protect the womb.

The shedding of the lining of the womb will produce a withdrawal bleed, so you will probably have a “period” each month starting during week 4, shortly before you finish an EVOREL SEQUI pack.

EVOREL SEQUI should not be used by children.

EVOREL SEQUI should not be used for contraception.

2. What you need to know before you use EVOREL SEQUI

Do not use EVOREL SEQUI if:

- You are allergic (hypersensitive) to estradiol and/or norethisterone, or any of the ingredients in EVOREL 50 and EVOREL CONTI patches (see section 6: “*What EVOREL SEQUI contains*” below).
- You had, have or suspect that you have breast cancer.
- You have a family history of breast cancer.
- You suspect or have estrogens-dependent malignant tumours (e.g. cancer of womb lining) or pre-malignant tumours (e.g. untreated atypical womb lining overgrowth).
- You have undiagnosed vaginal bleeding.
- You are pregnant or breastfeeding.
- You have liver disease, or a history of liver disease as long as liver function tests have not returned to normal.
- You had or have venous thromboembolism (deep venous blood clots, blood clots in the lungs).
- You have known conditions that promote blood clotting.
- You have active or recent past stroke or heart attack.
- You have porphyria.
- You have depression, which is not well controlled with treatment.

- You have had depression with previous use of estrogen and/or progesterone/progestogen containing medicines.

Warnings and precautions

Medical check-ups

- It is important that you have full and thorough physical and gynaecological examination and that your own family's medical histories regarding thrombosis (blood clots) are taken before you start any Hormone Replacement Therapy (HRT).
- You should receive regular full medical examinations whilst using EVOREL SEQUI.

A careful appraisal of the risk/benefit ratio should be undertaken before the initiation of long-term treatment.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Before you use EVOREL SEQUI, tell your doctor if:

- You are known to have inherited genetic changes called "BRCA1 and/or BRCA2 genes".
- You started your menstrual periods before the age of 12 years.
- You have a history of non-cancerous breast diseases such as atypical hyperplasia or lobular carcinoma *in situ*.
- You had any previous treatment using radiation therapy to the chest or breast.
- You have been treated or exposed while in your mother's womb to a medicine called diethylstilboestrol (DES).
- You are on treatment for depression.
- You have had depression with previous use of estrogen and/or progesterone/progestogen containing medicines.
- You have a substance abuse problem.
- You have underlying psychiatric disorder such as post-traumatic stress disorder or bipolar disorder.
- You have a family history of mental disorders.
- You have a history of physical or sexual abuse.

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, you should be closely

supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with EVOREL SEQUI in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for blood clots
- Risk factors for estrogen dependent tumours, e.g. first degree relative with breast cancer
- High blood pressure
- Liver disorders (e.g. benign tumour of the liver)
- Diabetes mellitus
- Gall stones
- Migraine or severe headache
- Systemic lupus erythematosus (lupus)
- A history of endometrial overgrowth (endometriosis)
- Epilepsy
- Breast disease

Conditions which require monitoring by your doctor while on estrogen therapy:

- Fluid retention (swelling) from estrogens, such as in EVOREL SEQUI.
- If you have heart or kidney malfunction, it should be carefully monitored.
- Disturbances of liver function.
- History of yellowing of skin and mucous membranes.
- Pre-existing high blood lipids. Rare cases of large increases of blood lipids leading to inflammation of the pancreas have been reported with estrogen therapy in this condition.

Stop using EVOREL SEQUI in case a contraindication is discovered and in the following situations:

- Skin yellowing or deterioration in liver function (jaundice).
- Increase in blood pressure.
- New onset of migraine-type headache.
- Pregnancy occurs.

Breast cancer

Breast cancer has been diagnosed slightly more often in women who use the Pill than in women of the same age who do not use the Pill. This slight increase in the numbers of breast cancer diagnoses gradually disappears during the course of the 10 years after stopping use of the Pill. When you are using EVOREL SEQUI, you must perform monthly breast self-

examinations. Your doctor will advise you on when to report for breast examinations and any appropriate investigations.

Ovarian cancer
Long- term use of estrogen containing HRT products such as in EVOREL SEQUI has been associated with an increased risk of ovarian cancer in some epidemiological studies.

Blood clots
If you have had a blood clot in the leg or lung, a stroke or a heart attack or are bed-ridden for any reason, such as after an operation, you may still be able to use EVOREL SEQUI, but your doctor should decide on this, and you should have a regular medical check-up with your doctor if you do use it. If, while using EVOREL SEQUI, you develop symptoms of a blood clot such as unexplained pains in the chest, abdomen or legs, the patch should be removed, and your doctor contacted immediately.

Heart Disease
The relative risk of heart disease during use of combined estrogen-progestogen HRT is increased.

Stroke
There is an increased risk of stroke in healthy women during treatment with HRT, such as EVOREL SEQUI.
Combined estrogen-progestogen and estrogen-only therapy are associated with an up to 1,5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age.

Depressed mood, depression and the risk of suicidality
Estrogen and/or progesterone/progestogen containing medicines including EVOREL SEQUI, may cause mood changes and depression, which may be severe. Severe depression is associated with 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. If you experience mood changes and depression, contact your doctor for advice.

Mental impairment
There is some evidence of probable dementia in women using continuous combined HRT such as EVOREL SEQUI.

EVOREL SEQUI should not be used for contraception.

Children and adolescents
EVOREL SEQUI should not be used by children.

Other medicines and EVOREL SEQUI
Always tell your health care provider if you are taking any other medicine (this includes all complementary or traditional medicines).
Some medicines can reduce the effect of EVOREL SEQUI such as, anti-epilepsy medicines (barbiturates, hydantoins, carbamazepine, meprobamate), phenylbutazone, rifampicin, rifabutin, bosentan, St. John's wort preparations (*Hypericum perforatum*) and certain medicines used for treatment of HIV infections and hepatitis, such as nevirapine and efavirenz.
Ritonavir and nelfinavir may reduce plasma concentrations of the estrogen component of EVOREL possibly resulting in a decrease in therapeutic effects and unscheduled bleeding. It may also reduce circulating concentrations of the progestin component of EVOREL SEQUI, which could result in a diminished protective effect against estrogen-induced endometrial hyperplasia.

If you are taking any of these medicines, tell your doctor. If you are taking other medicines on a regular basis, including medicines obtained without a prescription, the use of any of these medicines together with EVOREL SEQUI can cause undesirable interactions. Please consult your doctor, pharmacist or health care provider for advice.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before using this medicine.

Tell your doctor if you are pregnant, or think you are pregnant. You should not use EVOREL SEQUI during pregnancy.

You should not breastfeed when using EVOREL SEQUI.
Stop using EVOREL SEQUI immediately if you fall pregnant whilst using it.

Driving and using machines
There is no information about whether EVOREL SEQUI affects your ability to drive or use machines.

It is not always possible to predict to what extent EVOREL SEQUI may interfere with your daily activities. Do not engage in above activities until you are aware of the measure to which EVOREL SEQUI affects you.

3. How to use EVOREL SEQUI
Do not share medicines prescribed for you with any other person.
Always use EVOREL SEQUI exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

HRT treatment should not be continued for longer than 5 years.

When to use the patch
You MUST use the patches in the correct order as directed by your doctor.

- For **weeks 1 and 2** you should use the **EVOREL 50** patches
- As soon as you remove your last EVOREL 50 patch, replace it with one EVOREL CONTI patch
- For **weeks 3 and 4** you should use the **EVOREL CONTI** patches.

Start a new pack on EVOREL SEQUI as soon as you finish the current one. Do not leave a break between packs.

The instructions below apply to both EVOREL 50 and EVOREL CONTI patches:

- The patches must be changed at 3 or 4-day intervals.
- To make it easy to remember when this should be done, keep to the same two days every week. This will mean that one patch is on for three and the other for four days. For example, if you use your first patch on a Monday, it should be changed on Thursday and again on the following Monday.
- You can work out the two days of your own schedule from the following table, starting from the first day of use:

If you put your first patch on:

If you put your first patch on:	Change on:	Change again on:
Monday	Thursday	Monday
Tuesday	Friday	Tuesday
Wednesday	Saturday	Wednesday
Thursday	Sunday	Thursday
Friday	Monday	Friday
Saturday	Tuesday	Saturday
Sunday	Wednesday	Sunday

To help you to remember your "two patch change" days, mark them as shown:

Mon	**Tues**	**Wed**	**Thur**	**Fri**	**Sat**	**Sun**
Thur	**Fri**	**Sat**	**Sun**	**Mon**	**Tues**	**Wed**

How to put the EVOREL 50 and CONTI patches on

The patch should be applied to clean, dry skin but not on top of cuts, spots or other skin blemishes or on an area where you have just applied cream, moisturiser or talc.

The patch should be applied to the skin as soon as it is removed from the wrapper and applied as described below:

(a) Tear open the wrapper, first between the "V's" along one edge and then along the other edge. Take out the patch.

(b) With the backing foil facing you, bend the patch and peel off one half of the foil. **Do not touch the sticky side of the patch** otherwise it may not stick properly.

(c) Apply the open half of the patch to your skin, remove the other half of the foil and press down the rest of the patch.

(d) Press the patch with the palm of your hand to ensure it is firmly stuck to the skin.

(e) To remove, peel away an edge of the patch and pull smoothly away from the skin.

(f) You may use soap and water to help remove any gum/glue, which may remain on your skin after patch removal.

Where to place the patch

Stick the patch onto hairless area of skin below the waist. Most women prefer to wear the patch on the thigh or bottom. **It should never be worn on or near the breasts.** Although it can be worn underneath clothing, it should not be placed under elasticated waistbands.

The patch should not be placed on the same area of skin twice in a row.

What if the patch falls off?

Just apply a new patch of the **same type**, preferably taken from a spare pack. If this is not possible or leaves you without adequate supplies, contact your doctor.

Can I wash, bath or shower as normal?

YES, but do not scrub too hard in case you loosen the edges of the patch. It is recommended, however, that the patch be removed prior to a sauna bath, and that a new patch is applied immediately thereafter.

Can I go swimming with the patch on?

YES, the patch will not be affected.

Can I exercise or play sports?

YES, but try to avoid wearing it under tight clothing or waistband.

Can I sunbathe with the patch on?

YES, but keep the patch covered to avoid direct sunlight.

What if I am allergic to the patch?

Allergic reactions to the patch may occur. Should you have such a reaction, please consult your doctor.

Does the patch work as a contraceptive?

NO, the levels of hormone supplied by the EVOREL SEQUI patch are too low for it to do this. Although menopausal women face an ever-decreasing risk of pregnancy, normal precautions should be taken during sexual intercourse. If in doubt, talk to your doctor.

If you use more EVOREL SEQUI than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

Overdose with the patch is unlikely. Effects of too much EVOREL SEQUI can be reversed simply by removal of the patch. The most common symptoms of EVOREL SEQUI overdose are breast tenderness, nausea, irregular bleeding, stomach pain and/or bloating.

If you forget to use EVOREL SEQUI

If you forget to change the patch, change it as soon as possible and then keep to your original "patch change" days.

Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

4. Possible side effects

EVOREL SEQUI can cause side effects.

The side effects include the following:

Data from clinical trials:

Frequent:

- Depression
- Sleeplessness
- Nervousness
- Emotional incontinence (involuntary emotions)
- Headache
- High blood pressure
- Abdominal pain
- Digestive tract Disorder
- Feeling sick
- Itching
- Red skin rash
- Joint pain
- Breast pain
- Abnormal menstrual period (heavy and or prolonged)
- Painful menstruation
- Menstrual disorder (Irregular, heavy or prolonged bleeding from the vagina)
- Application site reaction – this includes sensitivity, redness, swelling and/or itchiness on the skin where the patch was placed
- Swelling may occur on the skin where the patch was placed
- Generalised feeling of discomfort
- Increased weight

Less frequent:

- Female breast cancer, non-cancerous (benign) tumour of breast

- Low sex drive, increased sex drive.
- Disturbance in attention, dizziness
- Excessive growth of womb lining, breakthrough bleeding or spotting
- Fatigue
- Suicidal thoughts/behaviour and suicide

Unwanted Effects Reported by EVOREL-treated Subjects in 15 Clinical Trials of EVOREL:

- Genital/vaginal fungal thrush infection
- Breast cancer
- Allergic reactions - sudden swelling of the face or throat which may cause difficulty in swallowing or breathing. This may be a sign of an allergic reaction
- Epilepsy
- Abnormal heart beat
- Blood clots in deep veins
- Frequent and loose watery stools with excessive gas in stomach or intestines
- Rash
- Muscle pain
- Generalised swelling
- Tissue oedema
- Pain

** Solicited signs/symptoms (recorded as yes/no) in 8 clinical trials of EVOREL.*

- Vaginal thrush
- Womb cancer
- Allergic reactions - sudden swelling of the face or throat which may cause difficulty in swallowing or breathing. This may be a sign of an allergic reaction
- Mood swings
- Stroke, migraine, burning or prickling sensation
- Abnormal heart beat
- Blood clots in deep veins of lower legs
- Blood clots in the lungs
- Abdominal distension
- Gall stones
- Stevens-Johnson syndrome (Extremely serious allergic reaction involving skin and mucous membranes)

- Back pain
- Breast enlargement
- Application site redness, application site itching, application site rash

If you develop skin rashes or irritation where you applied the patch, remove the patch and ask your doctor for advice.

Not all side effects reported for EVOREL SEQUI are included in this leaflet. Should your general health worsen or if you experience any other untoward effects while using this medicine, please consult your health care provider for advice.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor or pharmacist. You can also report side effects to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. By reporting side effects, you can help provide more information on the safety of EVOREL SEQUI.

5. How to store EVOREL SEQUI

Store all medicines out of reach of children.

EVOREL SEQUI should be stored at room temperature (i.e., at or below 25 °C). Do not freeze. Keep used and unused patches out of reach of children and pets. Put used patches in the bin you use for household rubbish. Do not flush down the toilet.

Other important information:

Do not use the patches:

⌦ After the expiry date shown on the label

⌦ If the protective sachet/pouch is open

Return all unused medicine to your pharmacist. Do not dispose of unused medicine in drains or sewerage systems (e.g., toilets).

6. Contents of the pack and other information

What EVOREL SEQUI contains

The active substances are estradiol and norethisterone.

Each pack of EVOREL SEQUI contains two types of patches:

- EVOREL 50
- EVOREL CONTI

Each **EVOREL 50** patch contains 3,2 mg of an estrogen called estradiol. Each EVOREL 50 patch delivers 50 micrograms of estradiol per 24 hours.

Each **EVOREL CONTI** patch contains 3,1 mg estradiol, formulated as 3,2 mg of estradiol hemihydrate and 9,82 mg norethisterone, formulated as 11,2 mg norethisterone acetate. Each patch delivers 50 micrograms of estradiol (an estrogen) and 170 micrograms of norethisterone (a progestogen hormone) per 24 hours.

EVOREL 50 AND CONTI patches contain the following inactive ingredients: Acrylate-vinylacetate copolymer (adhesive), guar gum (absorbent) and polyethylene terephthalate foil (backing film).

What EVOREL SEQUI looks like and contents of the pack

EVOREL SEQUI comes in a memory pack containing four EVOREL 50 patches and four EVOREL CONTI patches. Each patch comes in a protective sealed pouch.

EVOREL 50 and EVOREL CONTI patches are square shaped, transparent patches with a self-adhesive backing, which can be stuck to the skin.

EVOREL 50 is marked CE50 and has a surface area of 16 cm^2.
EVOREL CONTI is marked CEN1 and has a surface area of 16 cm^2.

In each patch the active ingredients are spread evenly in the adhesive and pass slowly through the skin into the body.

Holder of Certificate of Registration

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