

Package leaflet: Information for the user
Divigel 0.1% w/w Gel, 1 mg/dose
(estradiol)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

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

1. What Divigel is and what it is used for

Divigel is a Hormone Replacement Therapy (HRT). It contains the female hormone oestrogen.

Divigel is a smooth, opalescent (milky) alcohol based gel. When Divigel is applied to the skin the alcohol evaporates and the estradiol is absorbed through the skin and into the body.

Divigel is used for:

Relief of symptoms occurring after menopause

During the menopause, the amount of the oestrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ("hot flushes"). Divigel alleviates these symptoms after menopause. You will only be prescribed Divigel if your symptoms seriously hinder your daily life. You must talk to your doctor if you do not feel better or if you feel worse.

Prevention of osteoporosis

After the menopause some women may develop fragile bones (osteoporosis). You should discuss all available options with your doctor.

If you are at an increased risk of fractures due to osteoporosis and other medicines are not suitable for you, you can use Divigel to prevent osteoporosis after menopause.

2. What you need to know before you use Divigel

Medical history and regular check-ups

The use of HRT carries risks which need to be considered when deciding whether to start using it, or whether to carry on using it.

The experience in treating women with a premature menopause (due to ovarian failure or surgery) is limited. If you have a premature menopause the risks of using HRT may be different. Please talk to your doctor.

- Before you start (or restart) HRT, your doctor will ask about your own and your family's medical history. Your doctor may decide to perform a physical examination. This may include an examination of your breasts and/or an internal examination, if necessary. Once you have started on Divigel you should see your doctor for regular check-ups (at least once a year). At these check-ups, discuss with your doctor the benefits and risks of continuing with Divigel.

Regularly check your breasts for any changes (see 'Breast cancer' below). Go for regular breast screening, as recommended by your doctor.

Do not use Divigel if any of the following applies to you

If you are not sure about any of the points below, talk to your doctor **before using Divigel**,

Do not use Divigel if you:

- have or have ever had **breast cancer**, or if you are suspected of having it
- have **cancer which is sensitive to oestrogens**, such as cancer of the womb lining (endometrium), or if you are suspected of having it
- have any **unexplained vaginal bleeding**
- have **excessive thickening of the womb lining** (endometrial hyperplasia) that is not being treated
- have or have ever had a **blood clot in a vein** (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism)
- have a **blood clotting disorder** (such as protein C, protein S, or antithrombin deficiency)
- have or recently have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke or angina**
- have or have ever had a **liver disease** and your liver function has not returned to normal
- have a rare blood problem called "porphyria" which is passed down in families (inherited)
- are **allergic** (hypersensitive) to Estradiol (1mg/g as estradiol hemihydrate), or any of the other ingredients of Divigel (listed in section 6).

If any of the above conditions appear for the first time while using Divigel, stop using it at once and consult your doctor immediately.

Warnings and precautions

Talk to your doctor or pharmacist before using Divigel. Tell your doctor if you have ever had any of the following problems, before you start the treatment, as these may return or become worse during treatment with Divigel. If so, you should see your doctor more often for check-ups:

- fibroids inside your womb
- growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia)
- increased risk of developing blood clots (see 'Blood clots in a vein (thrombosis)')
- increased risk of getting an oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer)
- high blood pressure
- a liver disorder, such as a benign liver tumour
- diabetes
- gallstones
- migraines or severe headaches

- a disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE)
- epilepsy
- asthma
- a disease affecting the eardrum and hearing (otosclerosis)
- a very high level of fat in your blood (triglycerides)
- fluid retention due to cardiac or kidney problems.
- hereditary or acquired angioedema.

Children

Divigel can be accidentally transferred from the skin to other people. Do not allow others, especially children, to come into contact with the exposed area of your skin and cover the area, if needed, after the gel has dried. If a child comes into contact with the area of the skin where Divigel was applied, wash the child's skin with soap and water as soon as possible. Due to the estradiol transfer, young children may show signs of puberty that are not expected (for example breast budding). In most cases the symptoms will disappear when children are no longer exposed to Divigel.

Contact your healthcare provider if you see any signs and symptoms (breast development or other sexual changes) in a child that may have been exposed accidentally to Divigel.

Stop using Divigel and see a doctor immediately If you notice any of the following when taking HRT

- any of the conditions mentioned in the 'DO NOT use Divigel' section
- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease
- swollen face, tongue and/or throat and/or difficulty swallowing or hives, together with difficulty breathing which are suggestive of an angioedema
- a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness)
- migraine-like headaches which happen for the first time
- if you become pregnant
- if you notice signs of a blood clot, such as:
 - painful swelling and redness of the legs
 - sudden chest pain
 - difficulty in breathing.

For more information, see 'Blood clots in a vein (thrombosis)'.

Note: Divigel is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. Speak to your doctor for advice.

HRT and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)

Using oestrogen-only HRT will increase the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer).

Taking a progestogen in addition to the oestrogen for at least 12 days of each 28 day cycle protects you from this extra risk. So your doctor will prescribe a progestogen separately if you still have your womb. If you have had your womb removed (a hysterectomy), discuss with your doctor whether you can safely take this product without a progestogen.

In women who still have a womb and who are not taking HRT, on average, 5 in 1 000 will be diagnosed with endometrial cancer between the ages of 50 and 65.

For women aged 50 to 65 who still have a womb and who take oestrogen-only HRT, between 10 and 60 women in 1 000 will be diagnosed with endometrial cancer (i.e. between 5 and 55 extra cases), depending on the dose and for how long it is taken.

Divigel contains a higher dose of oestrogens than other oestrogen-only products. The risk of endometrium cancer when using Divigel together with a progesterone is not known.

Unexpected bleeding

If your doctor has prescribed you progestogen tablets in addition to Divigel you will usually have a bleed once a month (so-called withdrawal bleed) while taking Divigel. But, if you have unexpected bleeding or drops of blood (spotting) besides your monthly bleeding, which:

- carries on for more than the first 6 months
- starts after you have been taking Divigel for more than 6 months
- carries on after you have stopped taking Divigel

see your doctor as soon as possible.

Breast Cancer

Evidence shows that taking combined oestrogen-progestogen or oestrogen-only hormone replacement therapy (HRT) increases the risk of breast cancer. The extra risk depends on how long you use HRT. The additional risk becomes clear within 3 years of use. After stopping HRT, the extra risk will decrease with time, but the risk may persist for 10 years or more if you have used HRT for more than 5 years.

Compare

Women aged 50 to 54 who are not taking HRT, on average, 13 to 17 in 1 000 will be diagnosed with breast cancer over a 5-year period.

For women aged 50 who start taking oestrogen-only HRT for 5 years, there will be 16-17 cases in 1 000 users (i.e. an extra 0 to 3 cases).

For women aged 50 who start taking oestrogen-progestogen HRT for 5 years, there will be 21 cases in 1 000 users (i.e. an extra 4 to 8 cases).

Women aged 50 to 59 who are not taking HRT, on average, 27 in 1 000 will be diagnosed with breast cancer over a 10-year period.

For women aged 50 who start taking oestrogen-only HRT for 10 years, there will be 34 cases in 1 000 users (i.e. an extra 7 cases).

For women aged 50 who start taking oestrogen-progestogen HRT for 10 years, there will be 48 cases in 1 000 users (i.e. an extra 21 cases).

- **Regularly check your breasts. See your doctor if you notice any changes such as:**
 - dimpling of the skin
 - changes in the nipple
 - any lumps you can see or feel.

Additionally, you are advised to join mammography screening programs when offered to you. For mammogram screening, it is important that you inform the nurse/healthcare professional who is actually taking the x-ray that you use HRT, as this medication may increase the density of your breasts which may affect the outcome of the mammogram. Where the density of the breast is increased, mammography may not detect all lumps.

Ovarian cancer

Ovarian cancer is rare – much rarer than breast cancer. The use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of ovarian cancer.

The risk of ovarian cancer varies with age. For example, in women aged 50 to 54 who are not taking HRT, about 2 women in 2 000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be about 3 cases per 2 000 users (i.e. about 1 extra case).

Effects of HRT on heart and circulation

Blood clots in a vein (thrombosis)

The risk of **blood clots in the veins** is about 1.3 to 3- times higher in HRT users than in non-users, especially during the first year of taking it.

Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death.

You are more likely to get a blood clot in your veins as you get older and if any of the following applies to you. Inform your doctor if any of these situations applies to you:

- you are unable to walk for a long time because of major surgery, injury or illness (see also section 3, If you need to have surgery)
- you are seriously overweight (BMI >30 kg/m²)
- you have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots
- you or any of your close relatives has ever had a blood clot in the leg, lung or another organ
- you have systemic lupus erythematosus (SLE)
- you have cancer.

For signs of a blood clot, see “Stop using Divigel and see a doctor immediately”.

Compare

Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 in 1 000 would be expected to get a blood clot in a vein.

For women in their 50s who have been taking oestrogen-progestogen HRT for over 5 years, there will be 9 to 12 cases in 1 000 users (i.e. an extra 5 cases).

For women in their 50s who have had their womb removed and have been taking oestrogen-only HRT for over 5 years, there will be 5 to 8 cases in 1 000 users (i.e. 1 extra case).

Heart disease (heart attack)

There is no evidence that HRT will prevent a heart attack.

Women over the age of 60 years who use oestrogen-progestogen HRT are slightly more likely to develop heart disease than those not taking any HRT.

For women who have had their womb removed and are taking oestrogen-only therapy there is no increased risk of developing a heart disease.

Stroke

The risk of getting stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.

Compare

Looking at women in their 50s who are not taking HRT, on average, 8 in 1 000 would be expected to have a stroke over a 5-year period. For women in their 50s who are taking HRT, there will be 11 cases in 1 000 users, over 5 years (i.e. an extra 3 cases).

Other conditions

- HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.
- Women with a tendency to discoloration of the skin (chloasma) should minimise exposure to the sun or ultraviolet radiation whilst using Divigel.

Possible transfer of estradiol

During close skin contact estradiol gel may transfer to others (e.g. child, spouse, pets) if the application area has not been covered with clothing. Therefore, following precautions should be followed:

- wash your hands with soap and water after application
- cover the application area with clothing as soon as the gel has dried
- shower the application site before skin contact with others.

If the gel has accidentally transferred to others, wash the exposed area with soap and water. Contact your doctor or veterinarian in case of any symptoms of side-effects.

Other medicines and Divigel

Some medicines may interfere with the effect of Divigel. This might lead to irregular bleeding. This applies to the following medicines:

- Medicines for **epilepsy** (such as phenobarbital, phenytoin, and carbamazepine)
- Medicines for **tuberculosis** (such as rifampicin, rifabutin)
- Medicines for **HIV infection** (such as nevirapine, efavirenz, ritonavir and nelfinavir)
- Herbal remedies containing **St Johns wort** (*Hypericum perforatum*)

HRT can affect the way some other medicines work:

- A medicine for epilepsy (lamotrigine), as this could increase frequency of seizures
- Medicines for Hepatitis C virus (HCV) (such as combination regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir as well as a regimen with glecaprevir/pibrentasvir) may cause increases in liver function blood test results (increase in ALT liver enzyme) in women using CHCs containing ethinylestradiol. Divigel contains estradiol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using Divigel with this HCV combination regimen.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription, herbal medicines or other natural products. Your doctor will advise you.

Laboratory tests

If you need a blood test, tell your doctor or the laboratory staff that you are taking Divigel, because this medicine can affect the results of some tests.

Pregnancy, breast-feeding and fertility

Divigel is for use in post-menopausal women only. If you become pregnant, stop taking Divigel and contact your doctor.

Driving and using machines

No studies on the effects of Divigel on the ability to drive and use machines have been performed.

Divigel contains propylene glycol and ethanol

This medicinal product contains 62.5-187.5 mg propylene glycol in each 0.5-1.5 g dose.

This medicinal product contains 271-835 mg alcohol (ethanol) in each dose of 0.5-1.5g. It may cause burning sensation on damaged skin.

3. How to use Divigel

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will aim to prescribe the lowest dose to treat your symptom for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

The usual starting dose is 1.0 mg estradiol daily (one 1 g stick-pack per day). Divigel should be applied **once a day** to a clean, dry area of skin on your lower body, thighs or buttocks. Do not use Divigel where you have applied other creams or ointments on your skin. **Do not apply Divigel to the breasts, the face, broken or irritated skin, or the vaginal area.**

Cut or tear open the stick-pack, spread the gel over an area about 1-2 times the size of your hand and rub the gel gently into the skin. Apply the gel to a different side of your body each day. Allow the gel to dry for a few minutes after application. Do not wash this area for at least one hour after application.

Wash your hands immediately after applying the gel.

Do not allow other people to touch the area of the skin where the gel was applied until the gel has dried and cover with clothing if needed.

Avoid accidental contact of the gel with the eyes; if this occurs use plenty of cold water to flush the gel out of the eye(s).

If you have never used HRT before or you are changing from another period-free HRT product (continuous combined HRT), treatment with Divigel can be started on any day. If you are changing over from another type of HRT product such as cyclic HRT (oestrogen is given cyclically for 21 days with a treatment free period of 7 days) or sequential HRT (oestrogen is given continuously), you should start using Divigel the day after completing the 28 day cycle of HRT.

If you still have a womb, your doctor will normally also prescribe progestogen for you (usually a tablet taken for 12 to 14 days in each monthly cycle). After each course of progestogen, bleeding (like a period) will usually occur.

If you use more Divigel than you should

Overdose is unlikely but if you use more Divigel than your doctor has prescribed or if somebody else uses Divigel, talk to your doctor or pharmacist.

If in the unlikely event that Divigel is accidentally swallowed, you should seek medical advice from your doctor or pharmacist.

Signs of an overdose may include tender breasts, feeling bloated, anxious or irritable, feeling sick or being sick and withdrawal bleeding.

If you forget to use Divigel

If you miss a dose, apply it as soon as you remember unless the dose is more than 12 hours late. If it is more than 12 hours late, just skip the missed dose and continue the treatment at the same time on the next day. Missed doses may cause some vaginal bleeding or spotting (like a period).

If you stop using Divigel

If you want to stop using Divigel, talk to your doctor first. Your doctor will explain the effects of stopping treatment and discuss other possibilities with you.

If you need to have surgery

If you are going to have surgery, tell the surgeon that you are using Divigel. You may need to stop using Divigel about 4 to 6 weeks before the operation to reduce the risk of a blood clot (see section 2, Blood clots in a vein). Ask your doctor when you can start using Divigel again.

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

4. Possible side effects

Like all medicines, this medicine may cause side-effects although not everybody gets them. As with other skin gels, some patients may feel a slight cooling of the skin when applying Divigel.

Unwanted side effects tend to be most common during the first few months of treatment. These are usually mild, and should improve with continued treatment.

You should also tell your doctor if you have irregular bleeding or spotting during a course of treatment, and not just at the end of each cycle.

If you experience any of the following side effects you may have to stop using Divigel.

Tell your doctor immediately if you develop any of the following:

- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease
- a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness)
- migraine-like headaches which happen for the first time
- if you notice signs of a blood clot such as painful swelling and redness of the legs, sudden chest pain or difficulty in breathing.
- difficulty breathing or swelling of the face, mouth, or throat. You could be experiencing a serious allergic reaction.

The above side effects are serious and require immediate medical attention.

The following diseases are reported more often in women using HRT compared to women not using HRT:

- breast cancer
- abnormal growth or cancer of the lining of the womb (endometrial hyperplasia or cancer)
- ovarian cancer
- blood clots in the veins of the legs or lungs (venous thromboembolism)
- heart disease
- stroke
- probable memory loss if HRT is started over the age of 65.

For more information about these side effects, see section 2.

During the first few months of treatment, breakthrough bleeding, spotting and breast tenderness or enlargement can occur. These are usually temporary and normally disappear after continued treatment.

Other side effects include:

Common (affecting more than 1 person in 100):

- increased or decreased weight
- headache, dizziness
- feeling sick (nausea) or being sick, flatulence
- stomach pain/ cramps
- itchy, red skin, pain, increased sweating
- breast pain or tenderness
- irregular vaginal bleeding or spotting (like a period), menstrual disorder
- swelling of the ankles and legs.
- depression, nervousness, lethargy
- hot flushes

Uncommon (affecting more than 1 in 1 000 but less than 1 in 100):

- migraine, delusion, trembling
- changes in mood or sexual desire, anxiety, sleeplessness, apathy, emotional instability, impaired concentration, euphoria, agitation
- benign breast or endometrial tumour
- increased appetite
- high level of cholesterol in the blood
- increased heart rate
- constipation, digestive disturbance, diarrhoea, rectal disorder
- acne, hair loss (alopecia), dry skin, nail disorder, skin nodule, excessive growth of hair, a raised itchy rash that appears on the skin (urticaria), painful reddish skin nodules (erythema nodosum)
- joint disorders, muscle cramps
- increased urinary frequency/urgency, loss of bladder control, urinary tract infection, urine discoloration, blood in urine
- tender or swollen breast, abnormal growth of the lining of the womb, uterine disorder
- tiredness, abnormal laboratory test, weakness, fever, flu syndrome, general feeling of ill health
- sight problems, dry eye
- veins close to the surface of the body becoming swollen, tender, and red
- red or purple discolouration to the skin
- shortness of breath, stuffy or runny nose
- high blood pressure

Rare (affecting more than 1 in 10 000 but less than 1 in 1 000):

- skin rash
- blood clots, for example in the leg, pelvis or lungs
- problems with your liver
- problem tolerating contact lenses
- painful periods
- premenstrual like syndrome

Not known (cannot be estimated from the available data):

- uterine fibroids
- angioedema (a rare hereditary and acquired blood disorder that can cause swelling particularly in the face, hands and feet)
- memory problems or confusion caused by disrupted blood flow to the brain
- stomach ache, bloating
- liver disease causing yellowing of the skin
- contact rash, eczema

Divigel may affect the results of some blood tests, so make sure your doctor or the clinic performing the tests know you are using Divigel.

Dementia

HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

Other side effects of combined HRT

The following side effects have been reported with other HRTs:

- gall bladder disease and gallstones
- various skin disorders:
 - discolouration of the skin especially of the face or neck known as “pregnancy patches” (chloasma)
 - rash with target-shaped reddening or sores (erythema multiforme)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; or E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Divigel

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

Do not use Divigel after the expiry date which is stated on the carton and the stick-pack after Expiry Date. The expiry date refers to the last day of that month.

Do not store above 25 °C.

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

6. Contents of the pack and other information

What Divigel contains

The active ingredient of Divigel is estradiol (1mg/g as estradiol hemihydrate).

The other ingredients of Divigel are carbomer 974P, propylene glycol (E1520), trolamine, ethanol (alcohol) and purified water.

What Divigel looks like and contents of the pack

Divigel is a smooth, opalescent (milky) gel available in single dose aluminium foil sachets called stick-packs. Each stick-pack contains 1 g of gel.

Divigel is available in boxes of 28 x 1 g stick-packs.

Marketing Authorisation Holder:

Orion Corporation

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FIN-02200 Espoo, Finland

Manufactured by:

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20360 Turku, Finland

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

Orion Pharma (Ireland) Limited, c/o Allphar Services Ltd, 4045 Kingswood Road, Citywest Business Park, Co Dublin.

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