Rare (in less than 1 in 1,000, but more than 1 in 10,000 patients treated):

- intolerance to contact lenses
- pre-menstrual tension (PMT)
- feeling anxious
- migraine
- vomiting
- feeling bloated
- excessive hair growth
- acne
- muscle cramps
- vaginal discharge
- feeling tired
- swelling of the breasts
- change in sex drive

Very rare (in less than 1 in 10,000 patients treated, not known (cannot be estimated from the available data)):

- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia)

If unscheduled bleeding occurs after some time on HRT, you should contact your doctor. If unscheduled bleeding continues after stopping HRT, it may be necessary to perform tests to exclude disease of the endometrium (the lining of the uterus).

Changes can occur in the levels of certain proteins and hormones in the blood. The action of the hormones in the body is not affected. You should tell your doctor that you are taking HRT if you are to have a blood test.

The following side effects have been reported in association with estradiol treatment (frequency unknown):

- fibroids get bigger (growth in the womb increase)
- chorea (muscle twitches)
- worsening of fits (epilepsy)
- blood clots in the arteries (arterial thromboembolism)
- inflammation of the pancreas (pancreatitis) in women with pre-existing high levels of certain blood fats (hypertriglyceridemia)
- a condition where gastric juices, containing acid, travel back from the stomach into the oesophagus (gastroesophageal reflux disease) symptoms include heartburn
- liver disorders, which may include jaundice (yellowing of the skin)
- discolouration of the skin especially of the face or neck known as ''pregnancy patches'' (chloasma)
- rash with target shaped reddening or sores (erythema multiforme)
- skin discolouration (purpura)
- swelling of the skin around face and throat (angioedema)
- urinary incontinence
- painful/lumpy breasts (fibrocystic breast disease)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the **Google Play** or **Apple App Store**. By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE ZUMENON

- **KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.**
- Do not use after the expiry date printed on the carton label or blister strip.
- Do not store above 30°C. Keep in the original package.
- If your doctor tells you to stop using the medicine, please take it back to the pharmacist for safe disposal. Only keep the medicine if your doctor tells you to.
- If the medicine becomes discoloured or shows any other signs of deterioration, you should seek the advice of your pharmacist who will tell you what to do.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Zumenon contains

- Each film-coated tablet contains 2 mg of the active ingredient, estradiol (as the hemihydrate).
- Zumenon also contain the following inactive ingredients: Lactose, maize starch, hypromellose, magnesium stearate, titanium dioxide, black iron oxide (E172), colloidal anhydrous silica, talc, red iron oxide (E172), yellow iron oxide (E172) and macrogol 400.

What Zumenon looks like and contents of the pack

The tablets are brick red, round, biconvex, film-coated imprinted 379 on one side and blank on the other.

Zumenon tablets are available as calendar blister packs of 28 or 84 tablets.

Product Licence holder

Procured from within the EU and repackaged by the Product Licence holder: S&M Medical Ltd., Chemilines House, Alperton Lane, Wembley, HA0 1DX.

Manufacturer
These products are manufactured by Abbott Biologicals B.V., Veerweg 12, 8121 AA Olst, The Netherlands.

POM PL: 19488/0420

Leaflet revision date: 20 May 2024

Blind or partially sighted? Is this leaflet hard to see or read? Call 02087997607 to obtain the leaflet in large print, tape, CD or Braille.

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S420 Leaflet Zumenon 20240520

PACKAGE LEAFLET: INFORMATION FOR USER

ZUMENON® 2 mg TABLETS

(estradiol hemihydrate)

Your medicine is known as ZUMENON® 2 mg Tablets but will be referred to as Zumenon throughout the following leaflet.

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

1. WHAT ZUMENON IS AND WHAT IT IS USED FOR

Zumenon is a Hormone Replacement Therapy (HRT). It contains the female hormone oestrogen. Zumenon is used in postmenopausal women with at least 6 months since their last natural period and women switching from standard (cyclic or sequential) HRT on the advice of their doctor.

Zumenon 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"). Zumenon alleviates these symptoms after menopause. You will only be prescribed Zumenon if your symptoms seriously hinder your daily life.

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 Zumenon to prevent osteoporosis after menopause.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE ZUMENON

Medical history and regular check-ups

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

Go for regular breast screening, as recommended by your doctor.

Do not take Zumenon

If any of the following applies to you. If you are not sure about any of the points below, **talk to your doctor** before taking Zumenon,

Do not take Zumenon

- If you have or have ever had **breast cancer**, or if you are suspected of having it
- If you have **cancer which is sensitive to oestrogens**, such as cancer of the womb lining (endometrium), or if you are suspected of having it
- If you have any **unexplained vaginal bleeding**
- If you have **excessive thickening of the womb lining** (endometrial hyperplasia) that is not being treated.
- If you 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)
- If you have a **blood clotting disorder** (such as protein C, protein S, or antithrombin deficiency)
- If you have or recently have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke** or **angina**
- If you have or have ever had a **liver disease** and your liver function tests have not returned to normal
- If you have a rare blood problem called "porphyria" which is passed down in families (inherited)
- If you are **allergic** (hypersensitive) to oestradiol or any of the other ingredients of Zumenon (listed in section 6 Further information)

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

When to take special care with Zumenon

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 Zumenon. 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 a 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
- migraine 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 and acquired angioedema

Stop taking Zumenon and see a doctor immediately

If you notice any of the following when taking HRT:

- any of the conditions mentioned in the 'DO NOT take Zumenon' 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: Zumenon 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)

Taking 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 1000 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 1000 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.

Unexpected bleeding

You will have a bleed once a month (so-called withdrawal bleed) while taking Zumenon. 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 Zumenon more than 6 months
- carries on after you have stopped taking Zumenon

see your doctor as soon as possible

Breast cancer

Evidence shows that taking combined oestrogen-progestogen and 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 1000 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 1000 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 1000 users (i.e. an extra 4 to 8 cases).

Women aged 50 to 59 who are not taking HRT, on average, 27 in 1000 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 1000 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 1000 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.

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, on average about 2 women in 2000 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 2000 users (i.e. about 1 extra case).

Effect 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
- if 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 taking Zumenon and see a doctor immediately”.

Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 in 1000 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 1000 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 1000 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.

Looking at women in their 50s who are not taking HRT, on average, 8 in 1000 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 1000 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.

Other medicines and Zumenon

Some medicines may interfere with the effect of Zumenon. 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 John's 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.
  Zumenon contains estradiol instead of ethinylestradiol.
  It is not known whether an increase in ALT liver enzyme can occur when using Zumenon with this HCV combination regimen. Your doctor will advise you.

Problems due to high levels of the following medicines may occur when you take Zumenon so careful drug monitoring and dose decrease may become necessary:

- tacrolimus and cyclosporin – used, for example, for organ transplants
- fentanyl – a painkiller
- theophylline – used for asthma and other breathing problems

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.

Laboratory tests

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

Pregnancy and breast-feeding

Zumenon is for use in peri and postmenopausal women only. If you become pregnant, stop taking Zumenon and contact your doctor.

Zumenon contains lactose

Zumenon tablets contain milk sugar (lactose). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ZUMENON

Always take Zumenon exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Take one tablet every day, without a break between packs. Swallow the tablet with water, with or without food.

In women with a uterus, a progestogen should normally be added to Zumenon for 12 - 14 days of each month.

If you are having regular periods you should start taking Zumenon on day one of bleeding.

If you are not having regular periods and are not taking any other HRT preparations, or you are switching from a combined continuous HRT product, you can start taking Zumenon on any convenient day.

If you are currently using a ‘cyclic’ or ‘sequential’ HRT preparation (which involves taking an oestrogen tablet or patch for part of the month, followed by both oestrogen and progestogen tablet or patch for up to 14 days) start taking Zumenon the day after you finish the pack i.e. at the end of the progestogen phase.

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.

You may experience some irregular bleeding or light bleeding (spotting) during your first few months of taking Zumenon. If the bleeding is troublesome, or continues beyond the first few months of treatment you should discuss this with your doctor.

If you take more Zumenon than you should

Nausea (feeling sick), vomiting, sleepiness, dizziness and withdrawal bleeding may occur. No treatment is necessary, but if you are worried contact your doctor for advice.

If you forget to take Zumenon

Take the missed tablet as soon as you remember. If it is more than 12 hours since you took the last one, take the next dose without taking the forgotten tablet. Do not take a double dose. Bleeding or spotting may occur if you miss a dose.

If you need to have surgery

If you are going to have surgery, tell the surgeon that you are taking Zumenon. You may need to stop taking Zumenon 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 taking Zumenon again.

If you stop taking Zumenon

Do not stop taking Zumenon without first talking to your doctor.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

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 over the age of 65

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

The following serious side effects may occur during treatment with Zumenon:

- swelling of the skin around the face and neck. This may cause difficulty breathing.
- heart attack
- heavy, irregular or painful bleeds

If any of these side effects occur you should stop treatment immediately and contact your doctor.

The following side effects may occur during treatment:

Common (in less than 1 in 10, but more than 1 in 100 patients treated):

- headache
- feeling sick
- leg cramps
- abdominal pain
- pelvic pain
- unscheduled bleeding or spotting
- wind
- feeling weak (asthenia)
- weight changes
- rash or itching

Uncommon (in less than 1 in 100, but more than 1 in 1,000 patients treated):

- hypersensitivity (allergic) reaction such as skin rash, itching, skin redness
- hives
- painful reddish skin nodules (erythema nodosum)
- feeling down
- vaginal thrush (a vaginal infection due to a fungus called *Candida albicans*)
- high blood pressure
- swelling of the ankles, feet or fingers (peripheral oedema)
- water retention (oedema)
- peripheral vascular disease
- varicose veins
- blood clots in the veins of the legs or lungs (venous thromboembolism)
- gall bladder disorder
- back pain
- indigestion
- nervousness
- dizziness
- problems with your sight
- faster heart beat (palpitations)
- breast pain or tenderness

Rare (in less than 1 in 1,000, but more than 1 in 10,000 patients treated):

- intolerance to contact lenses
- pre-menstrual tension (PMT)
- feeling anxious
- migraine
- vomiting
- feeling bloated
- excessive hair growth
- acne
- muscle cramps
- vaginal discharge
- feeling tired
- swelling of the breasts
- change in sex drive

Very rare (in less than 1 in 10,000 patients treated, not known (cannot be estimated from the available data)):

- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia)

If unscheduled bleeding occurs after some time on HRT, you should contact your doctor. If unscheduled bleeding continues after stopping HRT, it may be necessary to perform tests to exclude disease of the endometrium (the lining of the uterus).

Changes can occur in the levels of certain proteins and hormones in the blood. The action of the hormones in the body is not affected. You should tell your doctor that you are taking HRT if you are to have a blood test.

The following side effects have been reported in association with estradiol treatment (frequency unknown):

- fibroids get bigger (growth in the womb increase)
- chorea (muscle twitches)
- worsening of fits (epilepsy)
- blood clots in the arteries (arterial thromboembolism)
- inflammation of the pancreas (pancreatitis) in women with pre-existing high levels of certain blood fats (hypertriglyceridemia)
- a condition where gastric juices, containing acid, travel back from the stomach into the oesophagus (gastroesophageal reflux disease) symptoms include heartburn
- liver disorders, which may include jaundice (yellowing of the skin)
- discolouration of the skin especially of the face or neck known as ‘‘pregnancy patches’’ (chloasma)
- rash with target shaped reddening or sores (erythema multiforme)
- skin discolouration (purpura)
- swelling of the skin around face and throat (angioedema)
- urinary incontinence
- painful/lumpy breasts (fibrocystic breast disease)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the **Google Play** or **Apple App Store**. By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE ESTRADIOL

- **KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.**
- Do not use after the expiry date printed on the carton label or blister strip.
- Do not store above 30°C. Keep in the original package.
- If your doctor tells you to stop using the medicine, please take it back to the pharmacist for safe disposal. Only keep the medicine if your doctor tells you to.
- If the medicine becomes discoloured or shows any other signs of deterioration, you should seek the advice of your pharmacist who will tell you what to do.

6. FURTHER INFORMATION

What Estradiol contains

- Each film-coated tablet contains 2 mg of the active ingredient, estradiol (as the hemihydrate).
- Estradiol also contain the following inactive ingredients: Lactose, maize starch, hypromellose, magnesium stearate, titanium dioxide, black iron oxide (E172), colloidal anhydrous silica, talc, red iron oxide (E172), yellow iron oxide (E172) and macrogol 400.

What Estradiol looks like and contents of the pack

The tablets are brick red, round, biconvex, film-coated imprinted 379 on one side and blank on the other.

Estradiol tablets are available as calendar blister packs of 28 or 84 tablets.

Product Licence holder

Procured from within the EU and repackaged by the Product Licence holder: S&M Medical Ltd., Chemilines House, Alperton Lane, Wembley, HA0 1DX.

Manufacturer
These products are manufactured by Abbott Biologicals B.V., Veerweg 12, 8121 AA Olst, The Netherlands.

POM PL: 19488/0420

Leaflet revision date: 20 May 2024

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S420 Leaflet Estradiol 20240520

PACKAGE LEAFLET: INFORMATION FOR USER

ESTRADIOL 2 mg TABLETS

(estradiol hemihydrate)

Your medicine is known as Estradiol 2 mg Tablets but will be referred to as Estradiol throughout the following leaflet.

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

1. WHAT ESTRADIOL IS AND WHAT IT IS USED FOR

Estradiol is a Hormone Replacement Therapy (HRT). It contains the female hormone oestrogen. Estradiol is used in postmenopausal women with at least 6 months since their last natural period and women switching from standard (cyclic or sequential) HRT on the advice of their doctor.

Estradiol 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"). Estradiol alleviates these symptoms after menopause. You will only be prescribed Estradiol if your symptoms seriously hinder your daily life.

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 Estradiol to prevent osteoporosis after menopause.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE ESTRADIOL

Medical history and regular check-ups

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

Go for regular breast screening, as recommended by your doctor.

Do not take Estradiol

If any of the following applies to you. If you are not sure about any of the points below, **talk to your doctor** before taking Estradiol,

Do not take Estradiol

- If you have or have ever had **breast cancer**, or if you are suspected of having it
- If you have **cancer which is sensitive to oestrogens**, such as cancer of the womb lining (endometrium), or if you are suspected of having it
- If you have any **unexplained vaginal bleeding**
- If you have **excessive thickening of the womb lining** (endometrial hyperplasia) that is not being treated.
- If you 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)
- If you have a **blood clotting disorder** (such as protein C, protein S, or antithrombin deficiency)
- If you have or recently have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke** or **angina**
- If you have or have ever had a **liver disease** and your liver function tests have not returned to normal
- If you have a rare blood problem called “porphyria” which is passed down in families (inherited)
- If you are **allergic** (hypersensitive) to oestradiol or any of the other ingredients of Estradiol (listed in section 6 Further information)

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

When to take special care with Estradiol

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 Estradiol. 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 a 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
- migraine 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 and acquired angioedema

Stop taking Estradiol and see a doctor immediately

If you notice any of the following when taking HRT:

- any of the conditions mentioned in the ‘DO NOT take Estradiol’ 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: Estradiol 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)

Taking 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 1000 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 1000 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.

Unexpected bleeding

You will have a bleed once a month (so-called withdrawal bleed) while taking Estradiol. 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 Estradiol more than 6 months
- carries on after you have stopped taking Estradiol

see your doctor as soon as possible

Breast cancer

Evidence shows that taking combined oestrogen-progestogen and 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 1000 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 1000 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 1000 users (i.e. an extra 4 to 8 cases).

Women aged 50 to 59 who are not taking HRT, on average, 27 in 1000 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 1000 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 1000 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.

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, on average about 2 women in 2000 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 2000 users (i.e. about 1 extra case).

Effect 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
- if 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 taking Estradiol and see a doctor immediately”.

Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 in 1000 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 1000 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 1000 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.

Looking at women in their 50s who are not taking HRT, on average, 8 in 1000 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 1000 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.

Other medicines and Estradiol

Some medicines may interfere with the effect of Estradiol. 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 John's 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.
  Zumenon contains estradiol instead of ethinylestradiol.
  It is not known whether an increase in ALT liver enzyme can occur when using Zumenon with this HCV combination regimen. Your doctor will advise you.

Problems due to high levels of the following medicines may occur when you take Estradiol so careful drug monitoring and dose decrease may become necessary:

- tacrolimus and cyclosporin – used, for example, for organ transplants
- fentanyl – a painkiller
- theophylline – used for asthma and other breathing problems

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.

Laboratory tests

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

Pregnancy and breast-feeding

Estradiol is for use in peri and postmenopausal women only. If you become pregnant, stop taking Estradiol and contact your doctor.

Estradiol contains lactose

Estradiol tablets contain milk sugar (lactose). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ESTRADIOL

Always take Estradiol exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Take one tablet every day, without a break between packs. Swallow the tablet with water, with or without food.

In women with a uterus, a progestogen should normally be added to Estradiol for 12 – 14 days of each month.

If you are having regular periods you should start taking Estradiol on day one of bleeding.

If you are not having regular periods and are not taking any other HRT preparations, or you are switching from a combined continuous HRT product, you can start taking Estradiol on any convenient day.

If you are currently using a ‘cyclic’ or ‘sequential’ HRT preparation (which involves taking an oestrogen tablet or patch for part of the month, followed by both oestrogen and progestogen tablet or patch for up to 14 days) start taking Estradiol the day after you finish the pack i.e. at the end of the progestogen phase.

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.

You may experience some irregular bleeding or light bleeding (spotting) during your first few months of taking Estradiol. If the bleeding is troublesome, or continues beyond the first few months of treatment you should discuss this with your doctor.

If you take more Estradiol than you should

Nausea (feeling sick), vomiting, sleepiness, dizziness and withdrawal bleeding may occur. No treatment is necessary, but if you are worried contact your doctor for advice.

If you forget to take Estradiol

Take the missed tablet as soon as you remember. If it is more than 12 hours since you took the last one, take the next dose without taking the forgotten tablet. Do not take a double dose. Bleeding or spotting may occur if you miss a dose.

If you need to have surgery

If you are going to have surgery, tell the surgeon that you are taking Estradiol. You may need to stop taking Estradiol 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 taking Estradiol again.

If you stop taking Estradiol

Do not stop taking Estradiol without first talking to your doctor.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

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 over the age of 65

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

The following serious side effects may occur during treatment with Estradiol:

- swelling of the skin around the face and neck. This may cause difficulty breathing.
- heart attack
- heavy, irregular or painful bleeds

If any of these side effects occur you should stop treatment immediately and contact your doctor.

The following side effects may occur during treatment:

Common (in less than 1 in 10, but more than 1 in 100 patients treated):

- headache
- feeling sick
- leg cramps
- abdominal pain
- pelvic pain
- unscheduled bleeding or spotting
- wind
- feeling weak (asthenia)
- weight changes
- rash or itching

Uncommon (in less than 1 in 100, but more than 1 in 1,000 patients treated):

- hypersensitivity (allergic) reaction such as skin rash, itching, skin redness
- hives
- painful reddish skin nodules (erythema nodosum)
- feeling down
- vaginal thrush (a vaginal infection due to a fungus called *Candida albicans*)
- high blood pressure
- swelling of the ankles, feet or fingers (peripheral oedema)
- water retention (oedema)
- peripheral vascular disease
- varicose veins
- blood clots in the veins of the legs or lungs (venous thromboembolism)
- gall bladder disorder
- back pain
- indigestion
- nervousness
- dizziness
- problems with your sight
- faster heart beat (palpitations)
- breast pain or tenderness