PACKAGE LEAFLET: INFORMATION FOR THE USER

TRIDESTRA®

Estradiol valerate and Medroxyprogesterone acetate

Read all of this leaflet carefully before you start taking 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.

In this leaflet:

1. WHAT TRIDESTRA IS AND WHAT IT IS USED FOR

Tridestra is a Hormone Replacement Therapy (HRT). It contains two types of female hormones, an oestrogen and a progestogen.

Tridestra is used for:

Relief of menopausal symptoms
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"). Tridestra alleviates these symptoms. You will only be prescribed Tridestra 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 Tridestra to prevent osteoporosis after menopause.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE TRIDESTRA

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 Tridestra 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 Tridestra.

Regularly check your breasts for any changes (see section 2, Breast cancer). Go for regular breast screening, as recommended by your doctor.

Do not take Tridestra
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 Tridestra.
Do not take Tridestra

- 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** to **Estradiol valerate** or **Medroxyprogesterone acetate** or any of the other ingredients of this medicine (listed in section 6)
- if you have been told that you have an intolerance to some sugars.

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

Warnings and Precautions
Talk to your doctor before starting the treatment if you have ever had any of the following problems, as these may return or become worse during treatment with Tridestra. 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
- 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 angioedema

Stop taking Tridestra 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 Tridestra' section
- 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 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: Tridestra 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).

The progestogen in Tridestra protects you from this extra risk.

Unexpected bleeding
You will have a bleed once every three months (so-called withdrawal bleed) while taking Tridestra. But, if you have unexpected bleeding or drops of blood (spotting) besides your three monthly bleed, which:
- carries on for more than the first 6 months
- starts after you have been taking Tridestra for more than 6 months
- carries on after you have stopped taking Tridestra

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 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 (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.

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).

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/m^2)
- 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
- you have had one or more miscarriages.

For signs of a blood clot, see "Stop taking Tridestra 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 1000 would be expected to get a blood clot in a vein.
For women in their 50s who have been taking oestrogen-progestogen HRT over 5 years, there will be 9 to 12 cases in 1000 users (i.e. an extra 5 cases).

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.

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 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.
- If you have a tendency to develop blotchy brown patches (chloasma) on the skin you should minimise exposure to the sun or ultraviolet radiation whilst using Tridestra.

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

- Medicines for **epilepsy** (such as phenobarbital, phenytoin and carbamazepin).
- 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).

Tell your doctor or pharmacist if you are taking, have recently taken or might take 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 Tridestra, because this medicine can affect the results of some tests.

Pregnancy and breast-feeding
• Pregnancy - If you become pregnant, stop taking Tridestra and contact your doctor.
• Breast-feeding – Do not take Tridestra if you are breast-feeding.

Tridestra with food and drink
Tridestra can be swallowed with a glass of water at the same time each day.

Driving and using machines
Tridestra should not affect your ability to drive or operate machinery.

Tridestra contains 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 TRIDESTRA

Always take 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.

If you are still having periods you should start to take the tablets on the fifth day of bleeding.

If you are not having periods or you are switching from a continuous combined HRT product you can start taking your tablets on any day.

If you are switching from a cyclic HRT product you should start taking Tridestra one week after you stop taking the other HRT product. Tridestra Tablets come in a calendar pack of 91 days. There are three blister strips numbered 1 to 3.
The pack is designed to help you to take your tablets correctly.
The white tablets are taken on days 1 - 70
The light blue, sometimes spotted tablets are taken on days 71 - 84.
The yellow tablets are taken on days 85 - 91.
- On the reverse side of strip number 3 you will see the heading “start day” and the seven days of the week.
- Pierce the foil below the day of the week when you start taking Tridestra. This will make it easy to check whether you have taken all tablets correctly according to schedule. Tablets 8, 15 etc are taken on the same week-day as the first tablet.
- The tablets are taken in sequence indicated by the numbers on the foil strips. Take one tablet each day following the numbers on the pack.

- Begin by taking tablet number 1 on strip number 1, moving on to strip number 2, then number 3 and ending with tablet 91.
- During the last week when you are taking the yellow tablets it is usual to have a menstrual like bleed.
- Swallow the tablets with a drink of water.
- Start the next pack of Tridestra the day after you finish this one. You should be starting each pack on the same day of the week.

Whilst taking this medicine
You should expect a regular menstrual type bleed every 3 months. This is quite normal even if your periods had stopped before. When you first start to take the tablets you may get some bleeding at odd times for a few months (see section 2, sub-heading 'Unexpected bleeding'). However, if this is still happening after a few months or if you experience heavy bleeding tell your doctor.

If you take more Tridestra than you should
If you or somebody else has taken too many Tridestra Tablets, tell your doctor or pharmacist.

If you forget to take Tridestra
It is best to take your tablet at the same time each day. If you forget, take it within 12 hours. If you do not remember and you are more than 12 hours late, leave the forgotten tablet. You should then continue by taking the next tablet at your usual time. Missing a tablet or irregular use of Tridestra tablets may cause unscheduled or breakthrough bleeding or spotting.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

If you need to have surgery
If you are going to have surgery, tell the surgeon that you are taking Tridestra. You may need to stop taking Tridestra 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 Tridestra 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 can cause side effects, particularly early on (in the first few months of treatment). However, not everybody gets them. These often disappear with continued treatment.

There are a number of situations in which you may have to **stop taking Tridestra.** Tell your doctor immediately if you develop any of the following conditions:
- you develop any of the conditions under 'section 2 Do not take Tridestra'
- yellowing of the skin or the whites of the eyes (jaundice). These may be signs of a liver disease
- you have been told that you have an increase in your blood pressure (symptoms may be headache, tiredness, dizziness)
- unexplained or first time migraine-type headaches, with or without disturbed vision (these headaches may be an early sign of a stroke)
- signs of a blood clot (see section 2 "Blood clots in a vein (thrombosis)) such as painful swelling and redness of the legs, sudden chest pain or difficulty breathing (these may be signs of a blood clot)
- a pain in your chest that spreads to your arm or neck (this pain could be a sign of heart disease).

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.

The following is a list of side effects that have been linked to the use of HRT:

Common: (may affect up to 1 in 10 people)
• weight increase or decrease, swelling caused by fluid retention
• depression, nervousness, lethargy
• nausea, vomiting, stomach cramps, flatulence
• headache, dizziness
• hot flushes, sweating
• breast tension and pain, vaginal discharge, bleeding or spotting, disorder of vulva/vagina, menstrual disorder.

Uncommon: (may affect up to 1 in 100 people)
• non-cancerous breast tumor, benign growths in the lining of the womb
• allergic (hypersensitivity) reaction
• increased appetite, high level of cholesterol in the blood
• anxiety, inability to sleep, apathy, mood swings, poor concentration, changes in sex drive and mood, euphoria, agitation
• migraine, sensation of tingling, pricking or numbness in skin, trembling
• visual impairment, dry eye
• unusually fast or irregular heartbeat
• increased blood pressure, superficial inflammation of the veins, redness or red spots on the skin
• breathlessness, runny or blocked nose
• constipation, indigestion/heartburn, diarrhoea, rectal disorder
• acne, hair loss, dry skin, nail problems, skin nodule, excessive hair growth (hirsutism), painful reddish skin nodules (*erythema nodosum*), generalised itchy rash
• joint disorders, muscle cramps
• increased and frequent urge to pass urine, loss of bladder control, bladder infections, discoloured urine, blood in the urine
• breast enlargement, breast tenderness, thickening of the lining of the womb, uterine disorder
• tiredness, abnormal laboratory tests, weakness, fever, flu-like symptoms, feeling generally unwell

Rare: (may affect up to 1 in 1,000 people)
• contact lens intolerance
• alternations in liver function and biliary flow
• skin rash
• blood clots in the veins of the legs or lungs
• menstrual pain, pre-menstrual like syndrome

Other side effects reported (frequency cannot be estimated from the available data)
- uterine fibroids
- worsening of the symptoms of hereditary angioedema
- reduced oxygen flow to the brain or to a section of the brain
- stomach pain, bloating, yellowing of the skin or eyes
- eczema
- gall bladder disease
- various skin disorders:
  - discoloration 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard. By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE TRIDESTRA

Keep this medicine out of the sight and reach of children. Do not use this medicine after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

Store this medicine at room temperature not exceeding 25°C in a dry place.

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 protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Tridestra contains
The active substances are:
white tablet: 2 mg estradiol valerate
light blue, sometimes spotted tablet: 2 mg estradiol valerate and 20 mg medroxyprogesterone acetate
yellow tablets do not contain any active ingredients.

The other ingredients are:
white tablet: lactose, maize starch, gelatin, talc and magnesium stearate
light blue, sometimes spotted tablet: lactose, maize starch, magnesium stearate, gelatin and indigo carmine (E132)
yellow tablet: lactose, maize starch, gelatine, magnesium stearate and yellow iron oxide (E172).
Tridestra tablets are gluten free.

What Tridestra looks like and contents of the pack
Each pack contains 91 tablets, 70 white tablets, 14 light blue, sometimes spotted tablets and 7 yellow tablets.

Marketing Authorisation Holder:

Orion Corporation, Orionintie 1, FIN-02200, Espoo, Finland

Manufactured by:
Orion Corporation Orion Pharma, Tengströminkatu 8, 20360 Turku, Finland

Delpharm Lille Sas-Lys Lez Lannoy, Parc d' Activités Roubaix-Est, 22 rue de Toufflers, CS 50070, Lys Lez Lannoy 59452, France

Orion Corporation, Orion Pharma, Orionintie 1, FIN-02200, Espoo, Finland
Distributed in the UK by:
Orion Pharma (UK) Ltd., Oaklea Court, 22 Park Street, Newbury, Berks RG14 1EA, United Kingdom.

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