Package leaflet: Information for the user

Totelle 1 mg/0.125 mg coated tablet

Estradiol/trimegestone

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, pharmacist or nurse.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Totelle is and what it is used for

Totelle is a Hormone Replacement Therapy (HRT). It contains two types of female hormones, an oestrogen and a progestogen. Totelle is used in postmenopausal women with at least 1 year since their last natural period.

Totelle 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"). Totelle alleviates these symptoms after menopause. You will only be prescribed Totelle 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 Totelle to prevent osteoporosis after menopause.

2. What you need to know before you take Totelle

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 Totelle 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 Totelle.

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

Do not take Totelle
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 Totelle.
Do not take Totelle

- 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 or trimegestone** or any of the other ingredients of this medicine (listed in section 6)

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

Warnings and precautions

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 Totelle. 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 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. Products containing oestrogens may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema.

Stop taking Totelle 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 Totelle' 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
  - sudden partial or complete loss of vision or other symptoms like double vision or bulging of the eye

  For more information, see 'Blood clots in a vein (thrombosis)'
- if you experience symptoms of angioedema such as hives, generalised swelling of parts of the body, most particularly the face, tongue or throat; difficulty swallowing or breathing difficulties.

Note: Totelle 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 Totelle protects you from this extra risk.

Irregular bleeding
You may have irregular bleeding or drops of blood (spotting) during the first 3 to 6 months of taking Totelle. However, if the irregular bleeding:
- carries on for more than the first 6 months
- starts after you have been taking Totelle for more than 6 months
- carries on after you have stopped taking Totelle

see your doctor as soon as possible.

Breast cancer
Evidence suggests that taking combined oestrogen-progestogen and possibly also oestrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you take HRT. The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment.

Women aged 50 to 79 who are not taking HRT, on average, 9 to 14 in 1000 will be diagnosed with breast cancer over a 5 year period. For women aged 50 to 79 who are taking oestrogen-progestogen HRT over 5 years, there will be 13 to 20 cases in 1000 users (i.e. an extra 4 to 6 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-progestagen 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 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/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 any other organ
- you have systemic lupus erythematosus (SLE)
- you have cancer

For signs of a blood clot, see section “Stop taking Totelle 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).

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.

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 suffer from a lack of parathyroid hormone (hypoparathyroidism) oestrogens can sometimes cause low levels of calcium in the blood.

Other medicines and Totelle
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some medicines may interfere with Totelle reducing its effectiveness and result in a return of symptoms. This applies to the following medicines:
- Medicines for **epilepsy** (such as phenobarbital, phenytoin and carbamazepine)
- Medicines for **tuberculosis** (such as rifampicin)
- Medicines for **HIV infection** (such as ritonavir and nelfinavir)
- Herbal remedies containing **St John's Wort** (Hypericum perforatum)
- Steroid medicines for inflammation such as dexamethasone
- Medicines for **chronic hepatitis C** (such as telaprevir)

Some medicines may increase oestrogen levels and may cause a higher risk of side effects. This applies to the following medicines:
- Medicines for infections such as erythromycin or ketoconazole
- Medicines for peptic ulcers such as cimetidine

The oestrogens in Totelle may cause higher blood levels of some medicines such as:
- Medicines for treating depression or anxiety such as citalopram, imipramine and diazepam.

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

Pregnancy and breast-feeding
Totelle is for use in postmenopausal women only. If you become pregnant, stop taking Totelle and contact your doctor.

Driving and using machines
Taking Totelle does not affect your ability to drive or use machinery.

Totelle contains lactose and sucrose
This medicine contains lactose and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Totelle

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

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

You can start treatment with Totelle on any day you choose. If you are transferring from a sequential HRT product (an HRT product that gives you a monthly bleed), treatment should begin the day after finishing the last pack unless instructed otherwise by your doctor.

Take one tablet from your blister pack of Totelle every day.
When you have finished each blister pack, start the next blister pack the next day.

Swallow your tablet whole, with water. You can take it during or between meals. It is best to take your tablet at the same time each day; this will help remind you to take your tablet.

If you take more Totelle than you should

If you take too many tablets by accident, consult your doctor or pharmacist.

You may feel some nausea, vomiting, breast tenderness, dizziness, drowsiness/tiredness or experience vaginal bleeding or spotting.

If you forget to take Totelle
Do not worry if you forget to take your tablet - take it during the next 12 hours, otherwise discard it, and take the usual dose the next day. Then carry on with your usual tablet taking routine.

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

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

4. Possible side effects

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.

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

Very common side effects (may affect more than 1 in 10 people):
- Breast pain

Common side effects (may affect up to 1 in 10 people):
- Irritation/infection of the vagina (vaginitis)
- Depression
- Joint pain
- Leg cramps

- Breakthrough bleeding/spotting
- Painful periods
- Breast tenderness, breast enlargement, discharge from the nipple
- Changes in weight (increase or decrease)
- Increased levels of fats in the blood

Uncommon side effects (may affect up to 1 in 100 people):
- Vaginal fungal infection
- Changes in sex drive
- Mood changes
- Loss of intellectual functions (dementia)
- Dizziness
- Headache, migraine
- Anxiety
- Intolerance to contact lenses
- Blood clots in the veins or lungs
- Nausea
- Bloating
- Abdominal pain
- Gallbladder disease
- Hair loss
- Spots (acne)
- Itching
- Changes in menstrual flow
- Changes in cervical secretion, other changes in your cervix
- Fluid retention (oedema)

Rare side effects (may affect up to 1 in 1,000 people):
- Breast cancer
- Lumpy breasts due to fibroids
- Ovarian cancer
- Acceleration of growth of a type of brain tumour (benign meningioma)
- Serious allergic reactions, including hives (urticaria) and swelling of the skin (angioedema)
- Glucose intolerance
- Irritability
- Stroke
- Worsening of fits (epilepsy)
- Heart attack (myocardial infarction)
- Inflammation and blood clots in blood vessels in the skin
- Worsening of asthma
- Vomiting
- Inflammation of the pancreas (pancreatitis)
- Inflammation of the large intestine (ischaemic colitis)
- Discoloration of the skin specially of face or neck known as “pregnancy patches” (chloasma), dark patches on the skin (melasma)
- Excessive body or facial hair growth
- Rash
- Production of milk from the breasts when you are not pregnant (galactorrhoea)
- Increase in size of fibroids in the womb

Very Rare side effects (may affect up to 1 in 10,000 people):
- Cancer of the lining of the womb

- Enlargement of an overgrowth of blood vessels in the liver (hepatic hemangiomas)
- Worsening of an inherited blood disease (porphyria)
- Low levels of calcium in the blood
- Worsening of a disease where you have sudden uncontrolled movements (chorea)
- Blood clots in the blood vessels of the eye
- Yellowing of skin or eyes caused by a blockage of the bile ducts (cholestatic jaundice)
- A rash with target shaped reddening or sores (erythema multiforme)
- A rash with painful reddish skin nodules (erythema nodosum)
- Thickening of the womb lining
- Increase in blood pressure

The following side effect has been reported with other HRTs:
- Extensive bruising (vascular purpura).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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; 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 Totelle

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

Do not use Totelle after the expiry date which is stated on the outer carton and blister. The expiry date refers to the last day of the month.

Do not store above 30°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 protect the environment.

6. Contents of the pack and other information

What Totelle contains

- The **active substances** are estradiol and trimegestone;
- Each coated tablet contains 1.03 mg estradiol hemihydrate corresponding to 1.00 mg estradiol and 0.125 mg trimegestone.
- The **other ingredients** are, Lactose monohydrate, Macrogol 8000, Magnesium stearate, Talc, Anhydrous calcium sulfate, Carnauba wax, Indigo carmine aluminium lake (E132), Glycerol mono-oleates, Macrogol 20000, Microcrystalline cellulose, Pharmaceutical glaze (shellac), Povidone, Printing ink (Black iron oxide (E172), Shellac and Propylene glycol), Stearic acid, Sucrose, Titanium dioxide (E171)

What Totelle looks like and contents of the pack

28 blue, round, biconvex coated tablets printed with '1 /0.125' in blister packs (PVC/PE/ACLAR/Aluminium)
The pack sizes are 1 x 28 tablets and 3 x 28 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

The product authorisation holder:	**Manufacturer:**
Pfizer Healthcare Ireland 9 Riverwalk National Digital Park Citywest Business Campus Dublin 24	Pfizer Ireland Pharmaceuticals Little Connell Newbridge County Kildare Ireland

This medicinal product is authorised in the Member States of the EEA under the following names:

Ireland, Sweden: Totelle coated tablet

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