

Package leaflet: Information for the patient

Livial® 2.5 mg tablets

tibolone

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions or need more advice, ask your doctor, family planning nurse or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them.
- If any of the side effects gets severe, or if you notice any not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

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

1. What Livial is and what it is used for

Livial is a Hormone Replacement Therapy (HRT). Livial contains tibolone, and is used in postmenopausal women with at least 12 months since their last natural period.

Livial is used for:

Relief of symptoms occurring after menopause

During the menopause, the amount of estrogen, produced by a woman’s body, drops. This can cause symptoms such as hot face, neck and chest (“hot flushes”). Livial alleviates these symptoms after menopause. You will only be prescribed Livial if your symptoms seriously hinder your daily life.

If indicated:

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 take Livial to prevent osteoporosis after menopause.

In section 6 “Contents of the pack and other information” you can find more information about Livial and what it is used for.

2. What you need to know before you use Livial

Medical history and regular check-ups

The use of HRT or Livial 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 or Livial may be different. Please talk to your doctor.

Before you start (or restart) HRT or Livial, 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've started on Livial, you should see your doctor for **regular check-ups** (at least once a year). During these check-ups, your doctor may discuss with you the benefits and risks of continuing with Livial.

Be sure to:

- go for **regular breast screening** and **cervical smear** tests
- **regularly check your breasts** for any changes such as dimpling of the skin, changes in the nipple, or any lumps you can see or feel.

Do not take Livial

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 Livial.

Do not take Livial

- if you are **pregnant**, or think you may be pregnant
- if you are **breastfeeding**
- if you have or ever had **breast cancer**, or if you are suspected of having it
- if you have **cancer which is sensitive to estrogens**, 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 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 **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 **tibolone**, or any of the other ingredients in Livial tablets (listed in section 6)

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

Warnings and precautions

When to take special care with Livial

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 Livial. If so, you should see your doctor more often for check-ups:

- fibroids inside your womb
- growth of the womb lining outside your womb (endometriosis) or a history of excessive growth of the lining of the womb (endometrial hyperplasia)
- increased risk of developing blood clots (see “Blood clots in a vein (thrombosis)”)
- increased risk of getting an estrogen-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

Stop taking Livial and see a doctor immediately

If you notice any of the following when taking HRT or Livial:

- any of the conditions mentioned in the “Do not take Livial” section
- yellowing of the skin or the whites of your eyes (jaundice),as these may be signs of 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: Livial 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).

There have been reports and studies of an increased cell growth or cancer of the lining of the womb in women using Livial. The risk of cancer of the lining of the womb increases the longer you take the medicine.

Irregular bleeding

You may have irregular bleeding or drops of blood (spotting) during the first 3-6 months of taking Livial.

However, if the irregular bleeding:

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

see your doctor as soon as possible.

Breast cancer

Evidence shows that taking tibolone increases the risk of breast cancer. The extra risk depends on how long you use tibolone. In studies with HRT, after stopping HRT the extra risk decreased with time, but the risk may persist for 10 years or more when women have used HRT for more than 5 years. No data for persistence of risk after stopping are available for tibolone, but a similar pattern cannot be ruled out.

Compare

Women taking **Livial** have a lower risk than women using combined HRT and a comparable risk with estrogen-only HRT.

Regularly check your breasts. See your doctor if you notice any changes such as:

- dimpling or sinking 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-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).

With use of Livial, the increased risk of ovarian cancer is similar to other types of HRT.

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 apply to you:

- you are pregnant or recently had a baby
- you use estrogens
- 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 Livial 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 estrogen-progestogen HRT for over 5 years, there will be 9 to 12 cases in 1000 users (i.e.an extra 5 cases).

With use of Livial, the increased risk of getting a blood clot in a vein is lower than with other types of HRT.

Heart disease (heart attack)

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

Women over the age of 60 who use estrogen-progestogen HRT are slightly more likely to develop heart disease than those not taking any HRT. As the risk of heart disease strongly depends on age, the number of extra cases of heart disease due to use of estrogen-progestogen HRT is very low in healthy women close to menopause, but will rise with more advanced age.

There is no evidence to suggest that the risk of myocardial infarction with Livial is different to the risk of other HRT.

Stroke

Recent research suggests that HRT and Livial increases the risk of having a stroke. This increased risk has mainly been observed in elderly postmenopausal women over 60 years of age.

Compare

Looking at women in their 50s who are not taking Livial – on average, over a 5 year period,

3 in 1000 would be expected to have a stroke. For women in their 50s who are taking Livial, the figure would be 7 in 1000 (i.e. an extra 4 cases).

Looking at women in their 60s who are not taking Livial – on average, over a 5 year period, 11 in 1000 would be expected to have a stroke. For women in their 60s who are taking Livial, the figure would be 24 in 1000 (i.e. an extra 13 cases).

Other conditions

- If you suffer an intolerance to some sugars, contact your doctor before using Livial.
- HRT is not intended to prevent pregnancy.
- Treatment with Livial results in a reduction in “good” cholesterol levels, depending on the dose administered. Levels of “bad” cholesterol remain unchanged.
- The hormone, estrogen, may cause your body to retain fluid, therefore care should be taken if you suffer heart or kidney problems.
- Patients with pre-existing high levels of fat (or triglycerides) in their blood, should be monitored closely during HRT, as treatment can (in rare cases) cause large increases in triglyceride levels, which can lead to pancreatitis (inflammation of the pancreas).
- Use of Livial leads to a very minor decrease in glycoproteins which affect levels of steroid hormones in the body, such as thyroid and sex hormones. Corticosteroid and cortisol hormone levels are unaffected. Steroid hormones are needed to enable the smooth functioning of a number of physiological functions in the body.
- 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.

Using other medicines

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

- medicines against **blood clotting** (such as warfarin)
- medicines for **epilepsy** (such as phenobarbital, phenytoin and carbamazepine)
- medicines for **tuberculosis** (such as rifampicin)
- herbal remedies containing **St John’s Wort** (Hypericum perforatum).

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.

Taking Livial with food and drink

You can eat or drink normally while you’re taking Livial.

Pregnancy and breast feeding

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

Driving and using machines

As far as is known, Livial has no effect on alertness and concentration.

Important information about some of the ingredients of Livial

Livial tablets contain 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 Livial

Livial is for oral use. Take one tablet each day. Swallow it with some water or other drink. Take the tablet at the same time each day.

The strips with Livial are marked with the days of the week. Start by taking the tablet marked with that day. For example, if it is Monday, take a tablet marked Monday on the upper row of the strip. Follow the days of the week until the strip is empty. Start the next strip the next day. Do not leave a break between strips or packs.

Livial should not be taken until twelve months after your last natural menstrual bleed. If Livial is taken sooner than this, the chance of irregular vaginal bleeding may be increased.

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

If you take more Livial than you should:

If you may have taken more Livial than you should, talk to a doctor or pharmacist immediately. If anybody takes too many tablets there is no need for great concern. However, you should talk to your doctor straight away. Signs of an overdose may include feeling sick, being sick or vaginal bleeding.

If you forgot to take Livial

If you forgot to take a tablet, take it as soon as you remember, unless you are more than 12 hours late. If you are more than 12 hours late just skip it. Do not take a double dose to make up for forgotten individual doses.

If you need to have surgery

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

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, Livial may have side effects. Most of these side effects are mild. Common side effects observed in clinical studies (occurring in 1-10% of the women using Livial) were:

- vaginal bleeding or spotting
- breast tenderness
- abdominal pain
- weight gain
- breast pain
- unnatural hair growth
- vaginal symptoms, such as discharge, itching, and irritation
- thickening of the lining of the womb or the lining of the cervix
- general itching
- vaginal thrush (overgrowth of yeast in the vagina)
- pelvic pain
- abnormal growth (potentially cancerous) of the cervix cells
- infection of the female genitals with vaginal discharge.

Uncommon side effects (occurring in 0.1-1% of the women using Livial) were:

- acne
- fluid retention
- abdominal discomfort

- breast discomfort
- fungal infection
- fungal infection of the vagina
- nipple pain

Other side effects observed with Livial in market use were:

- dizziness, headache, migraine, depression
- rash or itching
- visual disturbances
- gastro-intestinal upset
- joint pain, muscle pain
- changes in liver function
- skin condition caused by the excess secretion of oil from the skin glands

There have been reports of breast cancer and of an increased cell growth or cancer of the lining of the womb in women using Livial.

Tell your doctor if vaginal bleeding or spotting occurs, or if any of the above mentioned side effects become troublesome or continue.

The following side effects have been reported with other HRTs:

- gall bladder disease
- various skin disorders:
 - discoloration of the skin especially of the face or neck known as “pregnancy patches” (chloasma)
 - painful reddish skin nodules (erythema nodosum)
 - rash with target-shaped reddening or sores (erythema multiforme)

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,Website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Livial

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 blister and carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25 °C. Store in the original package in order to protect from light and moisture.

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 Livial contains

- The active substance is tibolone. Each tablet contains 2.5 mg tibolone.
- The other inactive ingredients are potato starch, lactose monohydrate, ascorbyl palmitate and magnesium stearate.

What Livial looks like and the contents of the pack

Livial tablets are white, round and flat with bevelled edges, with a diameter of 6mm, and marked “Organon” and an asterix on one side and “MK2” on the other side. Livial is available in packs of one or three blister strips each containing 28 or 30 tablets. Not all pack sizes may be marketed.

On the blister foil, weekday abbreviations may appear in Greek. Here is a translation of the weekdays in English and Greek:

<u>English</u>	<u>Greek</u>
Monday	ΔΕΥ
Tuesday	ΤΡΙ
Wednesday	ΤΕΤ
Thursday	ΠΕΜ
Friday	ΠΑΡ
Saturday	ΣΑΒ
Sunday	ΚΥΡ

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PCO Manufacturing Ltd., Unit 10, Ashbourne Business Park, Rath, Ashbourne, Co. Meath, Ireland.

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Manufacturer

N.V, Organon, Oss, The Netherlands or NV Organon, PO Box 20, 5340 BH Oss, The Netherlands or Organon (Ireland) Ltd, PO Box 2857, Drynam Road, Swords, Co. Dublin, Ireland.

Livial is a registered trademark of Merck Sharp & Dohme B.V.

Other information:

More about Livial

The most important natural sex hormones in women are estrogen and progesterone. These hormones are produced in the ovaries. They are needed for normal sexual development and control the menstrual cycle. The menopause is the time (usually around the age of 50) when the ovaries gradually stop producing estrogens. If the ovaries are removed surgically before the menopause, the decrease in hormone production occurs very quickly. The decrease in hormone production often leads to symptoms such as hot flushes and night sweats. The shortage of sex hormones may also cause the lining of the vagina to become thin and dry. So sexual intercourse may be painful and vaginal infections may occur more frequently. Some women also experience mood changes, nervousness, depression, irritability and loss of sexual desire.

Estrogens are also important for bone formation. Bone is built up during youth, and peak bone mass is reached between the age of 20 and 30. After that bone mass decreases at first slowly, but later in life more quickly, especially after the menopause. Gradually, the bones become brittle and may easily break (osteoporosis), especially in your spine, hips and wrists. Osteoporosis may also cause back pain, loss of height and a curved back.

Livial contains tibolone, a substance that has beneficial effects on different tissues in the body, such as brain, vagina and bone. This results in the relief of symptoms such as hot flushes and night sweats, and an improvement in the lining of the vagina, mood and sexual desire. Livial can also stop the process of bone loss that occurs in your spine, hip and wrists after the menopause. Unlike some hormone replacement therapies, Livial does not stimulate the lining of the womb. So treatment with Livial therefore does not cause monthly vaginal bleeding.

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