

Package leaflet: Information for the user

Livial® 2.5 mg tablets

tibolone

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.

In this leaflet:

- 1. What Livial is and what it is used for**
- 2. What you need to know before you take 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 2.5 mg tablet

The active substance is: tibolone.

This medicine is a hormone replacement therapy (HRT). It contains tibolone, a substance that has favourable effects on different tissues in the body, such as brain, vagina and bone. This medicine is used in postmenopausal women with at least 12 months (1 year) since their last natural period.

This medicine 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"). Livial alleviates these symptoms after menopause. You will only be prescribed this medicine 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 Livial to prevent osteoporosis after menopause.

There are three different kinds of HRT:

- **Oestrogen-only HRT**
- **Combined HRT**, containing two kinds of female hormone, an oestrogen and a progestogen.
- **Livial**, which contains a substance called tibolone

Livial is different from other HRT. Instead of actual hormones (such as oestrogen and progestogen) it contains tibolone. Your body breaks down tibolone to make hormones. Its effects and benefits are similar to combined HRT.

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 take Livial

For information on when you can start taking Livial, (including after a **hysterectomy**) see section 3.1 (overleaf).

Medical History and regular check-ups

The use of HRT or Livial carries risks that need to be considered when deciding whether to start taking it, or whether to carry on taking it. This is especially important if you are more than 60 years old.

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 taking 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.

→**Tell your doctor** if you have any medical problems or illnesses.

Regular check-ups

Once you have started on Livial, 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 Livial.

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

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.

2.1 Some women should not take Livial

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

- 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 tibolone or any of the other ingredients of this medicine (listed in section 6)
- If you are **pregnant** or think you might be pregnant.
- If you are **breastfeeding**.

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

If you have started the menopause you should not take Livial until **12 months after your last natural period**. If you take it sooner than this you may have irregular bleeding.

2.2 Warning and precautions

Talk to your doctor, pharmacist or nurse before taking Livial.

If you have ever had any of the following problems, tell your doctor 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 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

2.3 Stop taking Livial and see a doctor immediately

If you notice any of the following when taking Livial:

- any of the conditions mentioned in the "Do not take Livial" 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: 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.

2.4 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 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. But if the bleeding or spotting:

- 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've 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 oestrogen-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

→ Make an appointment to see your doctor as soon as possible

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.

2.5 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 **oestrogens**
- 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** ($BMI >30 \text{ kg/m}^2$)
- 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**.

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 oestrogen-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 oestrogen-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 oestrogen-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 slightly increases the risk of having a stroke. The increased risk is seen mainly in women over 60 years old. Other things that can increase the risk of stroke include:

- Getting older
- High blood pressure
- Smoking
- Drinking too much alcohol
- An irregular heartbeat

If you are worried about any of these things, talk to your doctor to see if you should take HRT

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).

2.6 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.

Livial is not intended for contraceptive use.

Treatment with Livial results in a marked dose-dependent decrease in HDL cholesterol (from - 16.7% with a 1.25 mg dose to -21.8% for the 2.5 mg dose after 2 years). Total triglycerides and lipoprotein(a) levels were also reduced. The decrease in total cholesterol and VLDL-C levels was not dose-dependent. Levels of LDL-C were unchanged. The clinical implication of these findings is not yet known.

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.

Treatment with Livial results in a very minor decrease of thyroid binding globulin (TBG) and total T4. Levels of total T3 are unaltered. Livial decreases the level of sex-hormone-binding globulin (SHBG), whereas the levels of corticoid binding globulin (CBG) and circulating cortisol are unaffected.

2.7 Other medicines and Livial

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*).

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, herbal medicines or other natural products.

2.8 Having an Operation

If you are going to have an operation, make sure your doctor knows about it. You may need to stop taking HRT about 4 to 6 weeks before the operation, to reduce the risk of a blood clot. Your doctor will tell you when you can start taking HRT again.

2.9 Livial with food and drink

You can eat or drink normally while you are taking Livial.

2.10 Pregnancy and breast-feeding

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

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

2.11 Driving and using machines

Livial has no known effect on the ability to drive or use machines.

2.12 Livial contains Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before using Livial.

If you are worried about anything in this section, talk to your doctor about the risks and benefits of HRT.

3. How to take Livial

3.1 When can you start taking Livial?

If it is not yet 12 months since your last natural period...	Wait before taking Livial (see section 2.1)...
If you are changing over from a period free HRT ... (see note below)...	Start taking Livial straight away
If you have never used HRT before	
If you were prescribed HRT because you have had a hysterectomy ...	
If you are being treated for endometriosis (a condition in which parts of the womb lining move around the body)...	Wait for your next period. Start taking Livial as soon as your period ends
If you are changing over from another type of HRT with which you have periods ... (see the note below)...	

If you are changing over from another type of HRT

There are several different types of HRT, such as tablets, patches and gels. Most contain either oestrogen, or oestrogen and progestogen. With some you still have periods, and with some you don't (*these are called period-free HRT*).

3.2 How to take Livial

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

The recommended dose is one tablet every day. Take this dose unless your doctor or pharmacist told you to do something different.

Press the tablet so that it comes through the foil. Swallow the tablet with some water or other drink, without chewing. **Take Livial at the same time each day.**

The strips of tablets are marked with the days of the week. Start by taking a tablet marked with the current day. For example, if it is Monday, take a tablet marked Monday on the top row of the

strip. Follow the arrows until the strip is empty. Start the next strip the next day. Do not leave a break between strips or packs.

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.

3.3 If you take more Livial than you should

It is unlikely that taking more than one tablet will do you any harm, but you may feel sick, be sick or have some vaginal bleeding.

3.4 If you forget to take Livial

If you forget 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, and take your next tablet at the usual time.
Don't take a double dose.

3.5 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, this medicine can cause side effects, although not everybody gets them. **Most side effects are mild.**

→**Tell your doctor or pharmacist** if you are worried about any side effects which you think may be due to Livial. (see also section 2.3, 'Stop taking Livial and see a doctor immediately')

4.1 Serious side effects – see a doctor straight away

If you think you may have signs of a serious side effect, see a doctor straight away.

You may need to stop taking Livial:

- If your **blood pressure** rises
- If your skin or the whites of your eyes go yellow (**jaundice**)
- If you suddenly have **migraine**-type headaches (see section 2.5 above)
- If you have signs of a **blood clot** (see section 2.5 above)
- If you get any of the problems listed in section 2.1 (Do not take Livial)

4.2 Other side effects

Common (may affect up to 1 in 10 women):

- breast pain
- stomach or pelvic pain
- unusual hair growth
- vaginal bleeding or spotting.

This is usually nothing to worry about in the first few months of taking HRT. If bleeding continues, or starts after you have been on HRT for a while see section 2.4.

- vaginal problems such as more secretions, itching, irritation and thrush
- thickening of the lining of the womb or the lining of the cervix
- weight gain.

Uncommon (may affect up to 1 in 100 women):

- swollen hands, ankles or feet – a sign of fluid retention
- stomach upset
- acne
- painful nipples or breasts feeling uncomfortable
- vaginal infections

Rare (may affect up to 1 in 1000 women):

- itchy skin

Some women taking Livial have also reported:

- depression, dizziness, headache
- joint pain or muscle pain
- skin problems such as rash or itching
- loss of vision or blurred vision
- changes in liver tests

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 any of the above mentioned side effects continues or becomes troublesome.

The following side effects have been reported with other HRTs:

- gall bladder disease
- various skin disorders:
 - discolouration 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 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 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 carton after ‘EXP’. The expiry date refers to the last day of that month.

Store below 25°C. Do not refrigerate. Store in the original package. Keep the blister in the outer carton, 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**.

The other 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, and marked Organon* on one side, and “MK2” on the other side. They come in packs of one or three strips of 28 tablets.

The Marketing Authorisation Holder is:

Organon Pharma (UK) Limited, Shotton Lane, Cramlington, United Kingdom, NE23 3JU.

The Manufacturer is:

NV Organon,
PO Box 20, 5340 BH Oss
Netherlands

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More about Livial

The most important natural sex hormones in women are oestrogens 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 oestrogens. 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.

Oestrogens 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, hip 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 the 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 does not cause monthly vaginal bleeding.

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 198 5000 (UK only)

Please be ready to give the following information:

Product name: Livial 2.5mg tablets

Reference number: PL 00025/0599

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