

**PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS REGULATIONS
(PREPARATIONS) 1986**

This medicine can be sold under doctor's prescription only

LIVIAL[®] 2.5 mg Tablets

Each Tablet contains:
Tibolone 2.5 mg

For a list of inactive ingredients see section 6.1 "What **LIVIAL** contains". See also section 2.3, "Important information about some of the ingredients of **LIVIAL**".

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

- Keep this leaflet. You may need to read it again.
- This leaflet contains concise information about **LIVIAL**. 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 medical condition seems similar to yours.

Important things to know about Hormone Replacement Therapy (HRT) and LIVIAL:

- HRT is used for relief of symptoms occurring after menopause and prevention of osteoporosis in postmenopausal women.
- **LIVIAL** is different from other HRT. Instead of actual hormones (such as oestrogen and progesterone) it contains tibolone. Your body breaks down tibolone to make hormones. Its effects and benefits are similar to combined HRT
- Some women should not take **LIVIAL** because of current medical problems or illnesses. Please read section 2.1 "DO NOT USE **LIVIAL**" and talk to your doctor before taking **LIVIAL**.
- Please tell your doctor before you start the treatment if you have ever had any of the problems listed in section "Special warnings concerning use of **LIVIAL**".

Therapeutic group: Urogenital system (including sex hormones).

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 consult 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.

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**.

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

1. WHAT IS THE MEDICINE INTENDED FOR?

This medicine is intended for:

- **Relief of symptoms occurring after menopause** (due to age or surgical intervention). **LIVIAL** can be used for the treatment of menopausal symptoms at least one year after menstruation has ceased.
If you are older than 60 years of age, you should only start **LIVIAL** if you are unable to take other treatments .
- **Prevention of osteoporosis** in postmenopausal women at high risk of future fractures which cannot use other medicine due to intolerance or contraindication.

At the time of the menopause (or after an operation to remove the ovaries), a woman's body stops producing the female hormone, oestrogen. Women may then suffer from symptoms such as hot flushes, night sweats, vaginal irritation and dryness, depression, and loss of sexual desire.

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

2. BEFORE USING THE MEDICINE

2.1 DO NOT USE 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 are **hypersensitive (allergic)** to tibolone or any of the other ingredients of this medicine (listed in section 6)
- 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, transient ischemic attack 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 **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.

Special warnings concerning use of LIVIAL

Talk to your doctor or pharmacist 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

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.

2.2 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-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 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 **oestrogens**
- you are **unable to walk** for a long time because of major surgery, injury or illness (see also "Having an operation")
- 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 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.

If you get a severe or sudden migraine-type headache, refer to your doctor as soon as possible.

The headache may be an early warning sign of a stroke.

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

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 during 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.

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.

Other medicines and LIVIAL

If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, you should tell the attending doctor or pharmacist. 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 carbamazepin)
- Medicines for **tuberculosis** (such as rifampicin)
- Herbal remedies containing **St John's Wort** (*Hypericum perforatum*).

Taking LIVIAL with food and drink

You can eat or drink normally while you are 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

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

2.5 Important information about some of the ingredients of LIVIAL

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** (see also section 6.1, "What **LIVIAL** contains?").

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

3. HOW DO YOU USE LIVIAL

Always take **LIVIAL** as instructed by the doctor. You should check with your doctor or pharmacist if you are unsure.

The dosage and treatment regimen will be determined by the doctor only.

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 section 3.1 "How to take LIVIAL" 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 changing over from another type of HRT with which you have periods ... (see section 3.1 "How to take LIVIAL" below)...	Wait for your next period. Start taking LIVIAL as soon as your period ends

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*).

3.1 How to take LIVIAL

The usually recommended dose is:

One tablet every day. Take this dose unless your doctor or pharmacist told you to do something different.

Do not exceed the recommended dose.

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.

There is no data regarding crushing/splitting/chewing of the tablets.

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.

If you have taken an overdose, or if a child has accidentally swallowed the medicine, proceed immediately to a hospital emergency room and bring the package of the medicine with you.

3.2 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.

Complete the full course of treatment as instructed by the doctor.

Even if there is an improvement in your health, do not discontinue use of this medicine before consulting your doctor.

Do not take medicines in the dark! Check the label and the dose each time you take your medicine. Wear glasses if you need them.

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

4. SIDE EFFECTS

Like all medicines, **LIVIAL** can cause side effects, although not everybody gets them.

Do not be alarmed by reading the list of side effects, you may not suffer from any of 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 if HRT is started over the age of 65

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

→**Tell your doctor or pharmacist** if you are worried about any side effects which you think may be due to **LIVIAL** (see also section “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 “Special warnings concerning use of **LIVIAL**” above)
- If you have signs of a **blood clot** (see section “Stop taking **LIVIAL** and see a doctor immediately” above)
- If you get any of the problems listed in section 2.1 (Do not take **LIVIAL**)

4.2 Additional side effects

Common side effects (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 2.2.

- 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 side effects (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 side effects (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)

If a side effect appears, if any of the side effects gets serious or if you notice a side effect not mentioned in this leaflet, consult your doctor.

Side effects can be reported to the Ministry of Health by using the online form for adverse events reporting which is on the Ministry of Health Homepage: www.health.gov.il or by following the link: [/http://sideeffects.health.gov.il](http://sideeffects.health.gov.il)

5. HOW TO STORE LIVIAL

- Avoid Poisoning! This medicine, as all other medicines, must be stored in a safe place out of the reach and sight of children and/or infants, in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use **LIVIAL** after the expiry date (exp. date) which is stated on pack. The expiry date refers to the last day of the indicated month.
- **Storage conditions:**
Store below 25°C, in a dry place protected from light.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

6.1 What LIVIAL contains?

The active substance is: Tibolone 2.5 mg.

In addition to the active ingredient, **LIVIAL** also contains:

Lactose monohydrate, potato starch, magnesium stearate, ascorbyl palmitate.

In addition, each tablet contains approximately 86.8 mg of lactose monohydrate.

6.2 What LIVIAL looks like and contents of the pack

The tablet is white, round and flat and marked with the word ORGANON* on one side and on the other side with the letters MK and beneath them the number 2.

Each box of **LIVIAL** contains 28 tablets.

Manufacturer:

N.V. Organon, Oss, The Netherlands.

License holder:

Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O.Box 7121, Petah-Tikva 49170.

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116.52.29486