יוני 2018

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

הנדון: Livial® 2.5 mg
לויאל 2.5 מ"ג

Dosage Form: tablets
Composition: tibolone 2.5 mg

חברת מרק שארפ ודוהם ישראל (MSD) מבקשת ליידע על עדכון העלון לרופא של התכשיר.

להלן לשון ההתוויה המאושרת לתכשיר:

- Complaints resulting from the natural or artificial menopause.

  Treatment of oestrogen deficiency symptoms in postmenopausal women, more than one year after menopause. Women above 60 years of age should only start with Livial treatment when they are intolerant of, or contraindicated for, other medicinal products approved for the treatment of oestrogen deficiency symptoms.

- Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. (See also section 5.1.)

For all women the decision to prescribe Livial should be based on an assessment of the individual patient's overall risks and, particularly in the over 60s, should include consideration of the risk of stroke (see sections 4.4 and 4.8).

למידע מלא, יש לעיין בעלון לרופא המאושר על ידי משרד הבריאות.

עדכונים מהותיים בעלון לרופא:
בפירוט שלהלן מופיע רק המידע המהותי שהתעדכן מתוך הפרק.
טקסט שהתווסף מודגש עם קו תחתון, טקסט שנמחק מופיע עם קו חוצה.

2 Qualitative and Quantitative composition

Each tablet contains 2.5 mg of tibolone.
Excipient (s) with known effect:
Each tablet contains approximately 86.8 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

4.3 Contraindications

…
Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4)

…

4.4 Special warnings and precautions for use

…
Evidence regarding the risks associated with HRT or tibolone in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

…

Ovarian cancer

~~Long-term (at least 5-10 years) use of estrogen-only HRT products in hysterectomized women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than estrogen-only products.~~

Ovarian cancer is much rarer than breast cancer.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies including the Women's Health Initiative (WHI) trial suggest that the use of combined HRTs may be associated with a similar or slightly smaller risk (see section 4.8).

In the Million Women Study it was shown that the relative risk for ovarian cancer with use of tibolone was similar to the risk associated with use of other types of HRT.

Venous thromboembolism

- Oestrogen or oestrogen-progestogen HRT is associated with a ~~higher relative~~1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. ~~One randomized controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users. For non-users it is estimated that the number of cases of VTE that will occur over a 5-year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years.~~ The occurrence of such an event is more likely in the first year of HRT than later~~. It is unknown whether Livial carries the same level of risk~~ (see section 4.8). In an epidemiological study using a UK database, the risk of VTE in association with tibolone was lower than the risk associated with conventional HRT, but only a small proportion of women were current users of tibolone and a small increase in risk compared with non-use cannot be excluded.
- Patients with known thrombophilic states have an increased risk of VTE and HRT or tibolone may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).
- Generally recognised risk factors for VTE include ~~a personal history or family history, severe~~ use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m^2)~~and~~, pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE. As in all postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT or tibolone 4 to 6 weeks earlier is recommended, if possible. Treatment should not be restarted until the woman is completely mobilised.
- ~~Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women~~ In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members

or if the defect is 'severe' (e.g, antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT or tibolone is contraindicated.

- Women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT or tibolone.
- ~~The risk of VTE may be temporarily increased with prolonged immobilization, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilization is liable to follow elective surgery, particularly abdominal surgery or orthopedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilized.~~

…

Coronary artery disease (CAD)

- ~~There is no evidence from randomized controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Oestrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomized controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.~~

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen or oestrogen-only HRT. In an epidemiological study using the GPRD no evidence was found of protection against myocardial infarction in postmenopausal women who received tibolone.

Other conditions

…

~~There is no conclusive evidence for improvement of~~ HRT does not improve cognitive function. There is some evidence ~~from the WHI trial~~ of increased risk of probable dementia in women who start using continuous combined ~~conjugated oestrogens and MPA~~ or oestrogen-only HRT after the age of 65. ~~It is unknown whether the findings apply to younger post-menopausal women or other HRT products.~~

4.5 Interaction with other medicinal products and other forms of interaction

Since Livial may increase blood fibrinolytic activity, it may enhance the effect of anticoagulants. This effect has been demonstrated with warfarin. Caution should therefore be exercised during the simultaneous use of Livial and anticoagulants, especially when starting or stopping concurrent Livial treatment. If necessary, the dose of warfarin should be adjusted.

~~*In vitro* studies revealed only minimal interaction of tibolone with cytochrome P_{450} enzymes. Therefore, Livial is not likely to play a clinically relevant inhibitory role on cytochrome P_{450} enzymes, nor is it likely that Livial is influenced by other drugs known to interact with cytochrome P450 enzymes.~~

There is limited information regarding pharmacokinetic interactions with tibolone. An *in vivo* study showed that simultaneous treatment of tibolone affects pharmacokinetics of the cytochrome P450 3A4 substrate

midazolam to a moderate extent. Based on this, drug interactions with other CYP3A4 substrates might be expected~~, however, the clinical relevance is dependent on the pharmacological and pharmacokinetic properties of the substrate involved.~~

Compounds that induce CYP3A4 activity such as barbiturates, carbamazepine, hydantoins and rifampicin may enhance the metabolism of tibolone and thus affect its therapeutic effect.

Herbal preparations containing St.John's wort (Hypericum Perforatum) may induce the metabolism of oestrogens and progestogens via CYP3A4. Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

4.6 Fertility, pregnancy and lactation

…

Fertility
In animal studies, Livial had anti-fertility activities by virtue of its hormonal properties.

4.8 Undesirable effects

…

Table 1 Undesirable effects of Livial

System organ class	**Common >1%,<10%**	**Uncommon >0.1%,<1%**	**Rare >0.01%,<0.1%**
Metabolism and nutrition disorders		Oedema**	
Gastrointestinal disorders	Lower abdominal pain	Abdominal discomfort**	
Skin and subcutaneous tissue disorders	Abnormal hair growth	Acne	Pruritus**

…

* The majority consisted of benign changes. Cervix pathology (cervical carcinoma) was not increased with ~~tibolone~~ Livial compared to placebo.

** These adverse reactions were identified through post-marketing surveillance. The frequency category was estimated based on relevant clinical trials.

In market use, other undesirable effects that have been observed include:dizziness, rash, ~~pruritus~~, seborrheic dermatosis, headache, migraine, visual disturbances (including blurred vision), ~~gastrointestinal upset~~, depression, ~~edema~~, effects on the musculoskeletal system such as arthralgia or myalgia and changes in liver function parameters.

Breast cancer

~~The MWS reported that, compared to never users, the use of various types of oestrogen-progestogen-combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88-2.12) than use of oestrogens alone (RR = 1.30, 95%CI: 1.21-1.40) or use of 2.5 mg tibolone (RR=1.45; 95%CI 1.25-1.68).~~
~~The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:~~

- ~~For women not using HRT or tibolone, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.~~
- ~~For 1000 current or recent users of HRT, the number of *additional* cases during the corresponding period will be~~

~~For users of *oestrogen-only* replacement therapy,~~
~~between 0 and 3 (best estimate = 1.5) for 5 years' use~~
~~between 3 and 7 (best estimate = 5) for 10 years' use~~
~~For users of *oestrogen-progestogen* combined HRT,~~
~~between 5 and 7 (best estimate = 6) for 5 years' use~~
~~between 18 and 20 (best estimate = 19) for 10 years' use.~~
~~For women who use tibolone the number of additional cases of breast cancer was comparable with that for oestrogen-only use.~~

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years.

  Any increased risk in users of *oestrogen-only* and tibolone therapy is substantially lower than seen in users of *oestrogen-progestogen* combinations

  - The level of risk is dependent on the duration of use (see section 4.4).
  - Results of the largest epidemiological study (MWS) are presented.

Table 2 Million Women study – Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1,000 never-users of HRT over a 5 year period*2	Risk ratio & 95%CI#	Additional cases per 1,000 HRT users over 5 years (95%CI)
Estrogen only HRT			
50-65	9-12	1.2	1-2 (0-3)
Combined estrogen-progestagen			
50-65	9-12	1.7	6 (5-7)
Tibolone			
50-65	9-12	1.3	3 (0-6)
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration of use.			

Endometrial cancer risk

Postmenopausal women with a uterus
The endometrial cancer risk is about 5 in every 1,000 women with a uterus not using HRT or tibolone.
…

Risk of ischaemic stroke

- The relative risk of ischaemic stroke is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of ischaemic stroke in women who use HRT or tibolone will increase with age, see section 4.4.

…

Other adverse reactions have been reported in association with oestrogen and oestrogen-progestogen treatment:

~~- Oestrogen-dependent neoplasms benign and malignant, e.g., endometrial carcinoma~~

~~- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among HRT users than among non-users. For further information, see sections 4.3 and 4.4~~

~~Myocardial infarction~~

- Ovarian cancer:

  Use of estrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).

  A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2,000 users. 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.
  In the Million Women Study, 5 years of HRT resulted in 1 extra case per 2,500 users.

- HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT (see section 4.4). Results of the WHI studies are presented:

Table 3 WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral estrogen-only*4			
50-59	7	1.2 (0.6-2.4)	1 (-3-10)
Oral combined estrogen-progestogen			
50-59	4	2.3 (1.2–4.3)	5 (1-13)

4 *Study in women with no uterus

- The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestogen HRT over the age of 60 (see section 4.4). There is no evidence to suggest that the risk of myocardial infarction with tibolone is different to the risk with other HRT

Table 4 WHI Studies combined - Additional risk of ischaemic stroke over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users over 5 yers
50-59	8	1.3 (1.1-1.6)	3 (1-5)

- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65 (see section 4.4)

בעלון לרופא היו עדכונים נוספים שאינם מהותיים ואינם נכללים בהודעה זו.

העלון לרופא מפורסם במאגר התרופות שבאתר האינטרנט של משרד הבריאות. ניתן לקבלם מודפסים על ידי פנייה לבעל הרישום, חברת MSD, בטלפון 09-9533333.

Livial מופץ ע"י חברת נובולוג בע"מ.

בברכה,
אורית בילין
רוקחת ממונה
MSD ישראל

References:
Israeli approved SPC Apr 2018