Available in Canada.

ᶜTibella® for the management of postmenopausal vasomotor symptoms.

ᶜTibella® (tibolone) is indicated for the short-term treatment of vasomotor symptoms due to estrogen deficiency in postmenopausal women, more than one year after menopause. Tibella® should only be prescribed to women with intact uteri.[1]

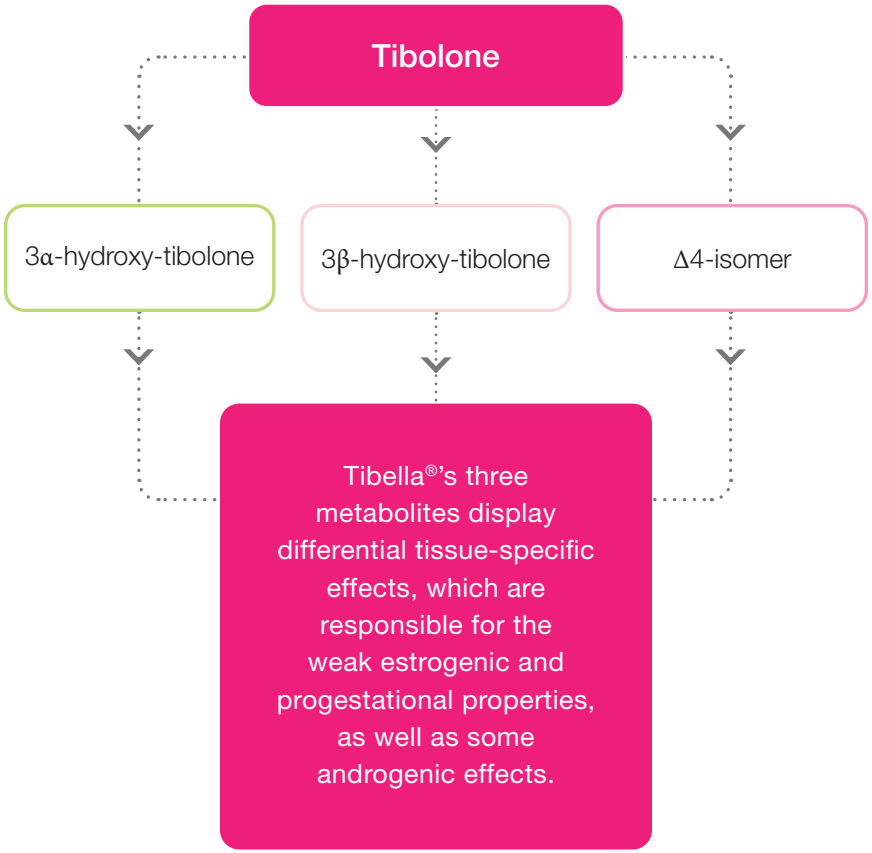
BioSyent

ᶜTibella®
(tibolone 2.5 mg tablets)

◊Tibella® – Mechanism of Action*

Tibella®'s 3 active metabolites display differential tissue-specific effects[1]

- The tibolone molecule is structurally related to the steroidal progestin norethynodrel.



Adapted from Product Monograph.
* Clinical significance unknown

◊Tibella® – Simple Dosing Regimen – one tablet once daily

Recommended Dose and Adjustments

- Tibella® dosage is one 2.5 mg tablet per day, every day.
- Maximum daily dose is 2.5 mg.
- Tablets should be swallowed whole with water or other drink, preferably at the same time every day. Tablets should not be broken or chewed.
- Tibella® may be taken with or without food.
- When one pack is complete, patients should start a new pack without missing any days.
- A separate progestogen should not be added to Tibella® treatment.
- No dose adjustment is necessary for the elderly. There is limited experience in treating women over age 65 years.
- **For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used*.**

Starting Tibella®

Tibella® can be started right away, if:

- Ovaries are surgically removed,
- It has been at least 12 months since last period, or
- The woman is treated with gonadotrophin releasing hormone (GnRH) analogues for endometriosis.

Switching to Tibella® treatment from a sequential or continuous combined HRT preparation

- Switching from sequential HRT preparation: Start the day following completion of prior regimen.
- Switching from continuous combined HRT: Tibella® may be started at any time.

* See Product Monograph for complete dosing and administration instructions

Missed Dose

- A missed dose should be taken as soon as remembered, unless it is more than 12 hours overdue.
- If more than 12 hours overdue, the missed dose should be skipped and the next dose taken at the normal time.
- Missing a dose may increase the likelihood of breakthrough bleeding/spotting.

Overdosage

- The acute toxicity of tibolone in animals is very low, therefore toxic symptoms are not expected to occur, even when several tablets are taken simultaneously
- In cases of acute overdose, nausea, vomiting and vaginal bleeding may occur in women.
- No specific antidote is known. Symptomatic treatment can be given if necessary.

Drug Interactions

There is limited information regarding pharmacokinetic interactions with tibolone.

- Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.
- Tibella® may enhance the effect of anticoagulants. Caution should be exercised during the simultaneous use of Tibella® and anticoagulants, especially when starting or stopping concurrent Tibella® treatment. If necessary, the dose of warfarin should be adjusted.
- Tibolone has shown a moderate effect on the pharmacokinetics of midazolam: drug interactions with other CYP3A4 substrates might be expected.
- CYP3A4 inducing compounds such as barbiturates, carbamazepine, hydantoins and rifampicin may enhance the metabolism of Tibella® and thus affect its therapeutic effect.

Serious Drug Interactions*

- Tibella® may increase blood fibrinolytic activity. This effect has been demonstrated with warfarin: concurrent use with anticoagulants should be monitored.
- St. John's Wort may induce metabolism of estrogens and progestogens via CYP3A4: may lead to changes in the uterine bleeding profile.

Serious Warnings and Precautions

Tibella® may increase the risk of stroke, breast cancer and, in women with an intact uterus, endometrial cancer, and can be dependent on individual risk factors.

A complete personal and family medical history should be taken before starting treatment with Tibella®. Periodic check-ups are recommended while on the treatment.

* Please see Product Monograph for complete drug-drug, drug-food and drug-laboratory interactions.

Tibella® – Common Adverse Events

The following are undesirable effects in 21 placebo-controlled studies (including the LIFT study) with 4079 women receiving therapeutic doses (1.25* or 2.5 mg) of tibolone, and 3476 receiving placebo.[1]

These undesirable effects occurred statistically significantly more frequently during treatment with tibolone than with placebo.

SYSTEM ORGAN CLASS	Common (≥1/100 –<1/10)
Gastrointestinal	Lower abdominal pain
Reproductive / Breast	Breast tenderness
	Cervical dysplasia
	Endometrial thickening
	Genital pruritis
	Pelvic pain
	Vaginal and Genital discharge
	Vaginal candidiasis
	Vaginal hemorrhage†
	Vulvovaginitis
Skin / Subcutaneous	Abnormal hair growth
Investigations	Weight increase
	Abnormal cervical smear

Adapted from Product Monograph
*1.25 mg is not an indicated dose in Canada
† bleeding that happens at least 12 months after periods have stopped

In a single placebo-controlled study that investigated tibolone for vaginal bleeding (separate from the adverse reaction results above):[1]

- Amenorrhea has been reported in 88% of women using tibolone 2.5 mg after 12 months of treatment.
- Breakthrough bleeding/spotting was reported in 32.6% of women in the first 3 months of treament, decreasing to 11.6% after 11-12 months.
- Women should be advised to report any breakthrough bleeding or spotting if it is still present after 6 months of treatment.

Clinical Use:

The decision to use Tibella® should be based on assessment of the patient's overall risks, including risk of stroke, particularly in patients over 60 years of age. Tibella® should be prescribed for the shortest duration consistent with treatment goals. Review the need for continuation of treatment after 6 months, taking into account the risk-benefit ratio for the individual user at that moment (including cardiovascular disease, endometrial cancer and breast cancer). Tibella® should only be continued as long as the benefit outweighs the risks.There is no authorized indication for pediatric use (≤18 years).

Contraindications:

- Liver dysfunction or disease with abnormal liver function tests.
- Known or suspected estrogen- or progestin-dependent malignant neoplasia.
- Endometrial hyperplasia.
- Known, suspected, or past history of breast cancer.
- Undiagnosed abnormal genital bleeding.
- Known or suspected pregnancy and/or lactation.
- Active or past history of arterial thromboembolic disease.
- Active or past history of venous thromboembolism or active thrombophlebitis.
- Known thrombophilic disorders.
- Partial or complete loss of vision due to ophthalmic vascular disease.
- Porphyria.
- Hypersensitivity to Tibella® or any of its ingredients or packaging.

Most Serious Warnings and Precautions:

- Tibella® may increase blood fibrinolytic activity therefore enhancing the effects of anticoagulants. This effect has been demonstrated with warfarin.
- St. John's wort (Hypericum perforatum) may induce the metabolism of estrogens and progestogens via CYP3A4. This may lead to changes in the uterine bleeding profile.
- **Stroke:** Tibella® may increase the risk of stroke.
- **Breast cancer:** Tibella® may increase the risk of breast cancer.
- **Endometrial cancer:** Tibella® may increase the risk of endometrial cancer in women with an intact uterus, and can be dependent on individual risk factors. A complete personal and family history should be taken before starting treatment; periodic check-ups are recommended while on treatment.

Estrogens with or without progestins:

- **should not** be prescribed for primary or secondary prevention of cardiovascular diseases
- should be prescribed at the **lowest effective dose**
- should be prescribed for the **shortest period** possible for the approved indication.

Other Relevant Warnings and Precautions:

- The risks of stroke, breast cancer and endometrial cancer should be carefully assessed.
- Evidence regarding the risks associated with HRT or tibolone in the treatment of premature menopause is limited.
- Patients with certain concomitant conditions should be closely supervised:
  - leiomyoma or endometriosis
  - risk for thromboembolic disorders
  - risk for estrogen-dependent tumours
  - hypertension
  - liver disorders
  - diabetes mellitus
  - cholelithiasis
  - migraine or severe headache
  - systemic lupus erythematosus
  - history of endometrial hyperplasia
  - epilepsy
  - asthma
  - otosclerosis
- Breakthrough bleeding
- Ovarian cancer
- Cardiovascular disease
- Driving
- Endocrine and metabolism
- Genitourinary
- Hepatic/biliary/pancreatic
- Immune
- Neurologic
- Renal
- Sexual health
- Pregnancy
- Immediate withdrawal of therapy: therapy should be discontinued when a contraindication is discovered, and in the following situations:
  - jaundice or deterioration in liver function
  - significant increase in blood pressure
  - new onset of migraine-type headache
  - pregnancy

For More Information:

Please consult the Tibella® Product Monograph available from Health Canada at https://pdf.hres.ca/dpd_pm/00051104.PDF for important information relating to adverse reactions, drug interactions and dosing information, or contact BioSyent at 1-888-439-0013.

◊Tibella® – for the treatment of postmenopausal vasomotor symptoms

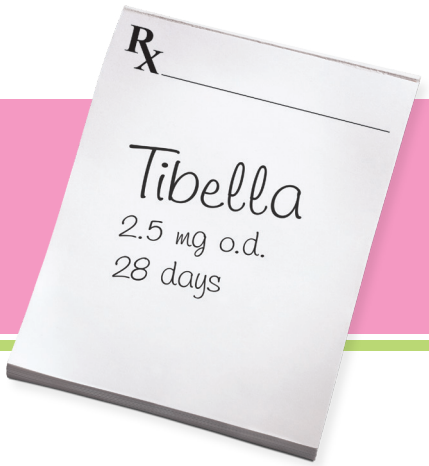
Tibella® has demonstrated:[1]

- Mechanism of action with weak estrogenic, progestogenic and some androgenic tissue-specific effects*
- Well-established safety and tolerability profile
- Significantly reduced vasomotor symptoms (flushing, sweating) vs. placebo

  Tibolone was significantly more effective in reduction of frequency of hot flushes and sweating episodes vs placebo; $p<0.001$†

† Landgren *et al.* Multicentre, double-blind, placebo controlled study in 775 postmenopausal women, randomized to receive tibolone 0.625 mg, 1.25 mg, 2.5 mg, 5.0 mg or placebo daily for 12 weeks. Main outcome measures were hot flushes, sweating, vaginal bleeding and side effects assessed at 4, 8 and 12 weeks. Approved dosage is 2.5 mg daily; 0.625, 1.25 and 5.0 mg doses are not recommended.

Simple dosing regimen one tablet once daily**



* Clinical significance unknown

**Please see Product Monograph for complete dosing recommendations

REFERENCES: 1. Tibella® Product Monograph, BioSyent Pharma Inc. May 2022. **2.** Landgren MB, *et al.* Dose–response analysis of effects of tibolone on climacteric symptoms. *BJOG: An International Journal of Obstetrics and Gynaecology*, Oct 2002, Vol.109,pp.1109-1114.

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REVIEWED BY PAAB

TB-230805E

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(tibolone 2.5 mg tablets)

1-888-439-0013