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Tibolone

Updated: December 12, 2013.

OVERVIEW

Introduction

Tibolone is a synthetic estrogen used for treatment of symptoms of menopause and prevention of osteoporosis. Tibolone has been associated with rare instances of acute, clinically apparent liver injury.

Background

Tibolone (tye' boe lone) is a synthetic estrogen-like steroid hormone which acts as an agonist of multiple type I steroid receptors and thus has weak estrogenic and progestational activities as well as some androgenic properties. The parent compound has no activity, but undergoes tissue-specific metabolism via a sulfatase to an active form which provides estrogenic effects without the need for concurrent progesterone administration. Tibolone also appears to have reduced estrogenic activity in breast tissue. It has been shown to be effective against the symptoms of menopause and in prevention of postmenopausal osteoporosis; it is approved in several European countries, but not the United States. Tibolone is available as 1.25 and 2.5 mg tablets under the brand name Livial. Side effects include vaginal bleeding, abdominal pain, weight gain, bloating, breast tenderness, genital pruritus and vaginitis.

Hepatotoxicity

In large scale prospective studies, tibolone has been associated with a low rate of transient serum aminotransferase levels, being greater than 3 times the upper limit of normal in 0.9% of tibolone versus 0.2% of placebo recipients, but instances of clinically apparent acute liver injury were not reported. In Europe, where tibolone has been in clinical use, there have been isolated reports of clinically apparent liver injury arising 6 to 12 months after starting and associated with a hepatocellular pattern of serum enzyme elevations and jaundice. Reported cases were self-limited and resolved within 2 to 6 months of stopping. Immunoallergic features were not present nor were autoantibodies.

Mechanism of Injury

The mechanism of liver injury due to tibolone is not known. The clinically apparent liver injury has not resembled that of the cholestatic jaundice associated with estrogens and has features of idiosyncratic liver injury.

Outcome and Management

The severity of liver injury due to tibolone has varied from mild, transient serum enzyme elevations to moderately severe acute hepatitis. No instances of acute liver failure, death, or chronic hepatitis have been linked

to tibolone use. A single instance of vanishing bile duct syndrome was reported after tibolone use in combination with St. John's wort. Rechallenge studies have not been done.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tibolone – Livial®

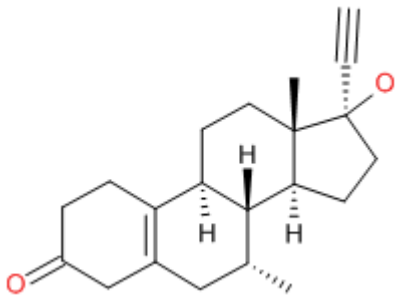
DRUG CLASS

Synthetic Estrogen

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Tibolone	5630-53-5	C21-H28-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 12 December 2013

Zimmerman HJ. Hormonal derivatives and related drugs. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 555-88.

(Expert review of hepatotoxicity published in 1999; estrogenic steroids and oral contraceptives are discussed, but not tibolone).

Chitturi S, Farrell GC. Adverse effects of hormones and hormone antagonists on the liver. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 605-19.

(Review of hepatotoxicity of estrogenic hormones; tibolone is not discussed).

Levin ER, Hammes SR. Estrogens and progestins. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1163-94.

(Textbook of pharmacology and therapeutics).

Blanco Sampascual S, de Las Heras Niño B, Cabezudo Gil P, Ruiz Eguiluz P, Orive Cura V. [Tibolone-induced hepatotoxicity]. Gastroenterol Hepatol 2002; 25: 274. Spanish. PubMed PMID: 11975880.

(51 year old woman developed jaundice and pruritus 1 year after starting tibolone [bilirubin 43.7 mg/dL, ALT 1800 U/L, Alk P 407 U/L], resolving within 6 months of stopping).

Swegle JM, Kelly MW. Tibolone: a unique version of hormone replacement therapy. Ann Pharmacother 2004; 38: 874-81. PubMed PMID: 15026563.

(Review of the structure, pharmacology, mechanism of action and clinical efficacy of tibolone, which has been available in Europe for several years, but not in the U.S.; side effects include vaginal bleeding, abdominal pain, weight gain, bloating, breast tenderness and vaginitis; no mention of hepatotoxicity).

Rigato I, Cravatari M, Avellini C, Ponte E, Crocè SL, Tiribelli C. Drug-induced acute cholestatic liver damage in a patient with mutation of UGT1A1. Nat Clin Pract Gastroenterol Hepatol 2007; 4: 403-8. PubMed PMID: 17607296.

(54 year old woman developed jaundice 6 months after starting tibolone and 2 months after starting flavoxate [bilirubin 12.7 mg/dL, ALT 1938 U/L, Alk P 244 U/L], resolving in 2 months of stopping both).

Bai W, Henneicke-von Zepelin HH, Wang S, Zheng S, Liu J, Zhang Z, Geng L, et al. Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: a randomized, double blind, parallel-controlled study versus tibolone. Maturitas 2007; 58: 31-41. PubMed PMID: 17587516.

(Controlled trial of tibolone vs black cohosh in 244 women with menopausal symptoms; "Adverse events that might have been interpreted as sign of a liver dysfunction did not occur").

Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, Mol-Arts M, et al.; LIFT Trial Investigators. The effects of tibolone in older postmenopausal women. N Engl J Med 2008; 359: 697-708. PubMed PMID: 18703472.

(Controlled trial of tibolone vs placebo in 4538 women with osteoporosis; ALT elevations >3 times ULN occurred in 0.9% on tibolone and 0.2% placebo, no mention of clinically apparent liver injury; the study was stopped because of increased incidence of stroke on tibolone).

Etogo-Asse F, Boemer F, Sempoux C, Geubel A. Acute hepatitis with prolonged cholestasis and disappearance of interlobular bile ducts following tibolone and Hypericum perforatum (St. John's wort). Case of drug interaction? Acta Gastroenterol Belg 2008; 71: 36-8. PubMed PMID: 18396749.

(57 year old woman developed jaundice 2 years after starting tibolone and 10 weeks after starting St. John's wort [bilirubin 6.3 rising to 37.0 mg/dL, ALT 424 U/L, Alk P 162 U/L, ANA 1:320], with slow improvement and biopsy indicating bile duct loss; authors suggested an interaction between herbal and tibolone).