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Elagolix

Updated: January 31, 2019.

OVERVIEW

Introduction

Elagolix is an oral, nonsteroidal gonadotropin releasing hormone (GnRH) antagonist that decreases estrogen production and is used to treat painful forms of endometriosis in women. Elagolix therapy is associated with a low rate of serum enzyme elevations during therapy and has yet to be linked to instances of clinically apparent liver injury.

Background

Elagolix (el ag" o lix') is a synthetic nonsteroidal antagonist of gonadotropin releasing hormone (GnRH) that blocks GnRH stimulation of luteinizing hormone (LH) and follicular stimulating hormone (FSH) production by the pituitary gland, thereby decreasing the synthesis of estrogen by the ovaries in women and testosterone by the testes in men. Elagolix has been found to be palliative in women with painful endometriosis with equivalent efficacy to the GnRH agonists such as leuprolide and goserelin. Because elagolix is an antagonist of GnRH, it does not cause the initial increase in estrogen synthesis that occurs with use of GnRH agonists. Elagolix was approved for use in the United States in 2018 and current indications are limited to therapy of painful forms of endometriosis. Elagolix is available under the brand name Orilissa as tablets of 150 and 200 mg. The typical dose is either 150 once daily (low dose therapy) or 200 mg twice daily (high dose therapy). The low dose regimen is recommended for women with moderate liver dysfunction (Child-Pugh Class B cirrhosis) and elagolix is considered contraindicated in patients with more advanced cirrhosis (Class C). Common side effects include symptoms typical of hypogonadism such as hot flashes, decreased libido, anxiety, headache, nausea, diarrhea, weight gain and fluid retention. Potential severe adverse reactions include acute hypersensitivity reactions, suicidal ideation and mood disorders, and significant bone loss with extended therapy.

Hepatotoxicity

Elagolix therapy has been associated with serum enzyme elevations in a small proportion of patients, rates of ALT elevations above 3 times the upper limit of normal being 0.2% with 150 mg once daily and 1.1% with 200 mg twice daily. The elevations, however, are generally mild and self-limited, resolving even without dose adjustment. Occasional patients require drug discontinuation because of serum enzyme elevations, but there were no instances of liver injury with jaundice or clinically apparent acute liver injury in the preregistration-controlled trials. Since its approval and more widescale use, there have been no published reports of clinically apparent liver injury attributed to elagolix.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which elagolix might cause liver injury is unknown. Elagolix has multiple complex interactions with several hepatic drug metabolizing enzymes, is a mild inducer and a substrate of CYP 3A4 and drug levels can be significantly increased by OATP1B1 and CYP 3A4 inhibitors.

Outcome and Management

Serum aminotransferase elevations during elagolix therapy are usually mild and self-limited, rarely requiring dose adjustment or drug discontinuation. Routine monitoring of liver tests is not recommended except in patients with known, preexisting liver disease. There is no evidence of cross sensitivity to liver injury among the various GnRH antagonists.

Drug Class: Obstetrical and Gynecological Agents, Gonadotropin Releasing Hormone Antagonists

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Elagolix – Orilissa®

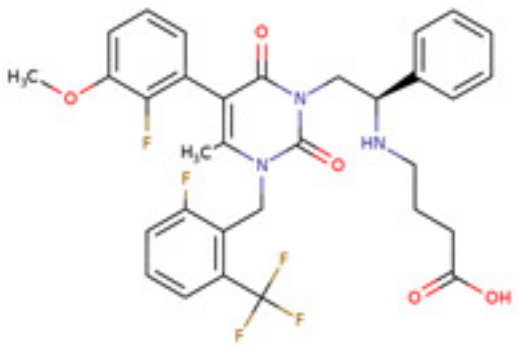
DRUG CLASS

Obstetrical and Gynecological Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Elagolix	834153-87-6	C32-H30-F5-N3-O5	

ANNOTATED BIBLIOGRAPHY

References updated: 31 January 2019

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 699.

(Expert review of hepatotoxicity published in 1999; the GnRH antagonists such as elagolix are not discussed).

Chitturi S, Farrell GC. Estrogen receptor antagonists. 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. 610-2.

(Review of hepatotoxicity of hormonal products; does not discuss the GnRH antagonists such as elagolix).

Isaacs C, Wellstein A, Riegel AT. Hormones and related agents in the therapy of cancer. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 20181, pp. 1237-47.

(Textbook of pharmacology and therapeutics).

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; mentions that moderate and severe liver dysfunction are associated with higher elagolix plasma levels, that serum aminotransferase elevations arise in a small proportion of patients and that there was no evidence of severe drug induced hepatotoxicity in the preregistration clinical studies).

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; mentions that moderate and severe liver dysfunction are associated with higher elagolix plasma levels, that serum aminotransferase elevations arise in a small proportion of patients and that there was no evidence of severe drug induced hepatotoxicity in the preregistration clinical studies).

Diamond MP, Carr B, Dmowski WP, Koltun W, O'Brien C, Jiang P, Burke J, Jimenez R, Garner E, Chwalisz K. Elagolix treatment for endometriosis-associated pain: results from a phase 2, randomized, double-blind, placebo-controlled study. Reprod Sci 2014; 21: 363-71. PubMed PMID: 23885105.

(Among 155 women with painful endometriosis treated with elagolix [150 or 250 mg daily] or placebo once daily for 12 weeks, pain scores decreased with elagolix treatment, but the differences from placebo were not statistically significant while adverse event rates were higher with elagolix than placebo for headache [8% and 10% vs 2%], nausea [6% and 10% vs 2%] and anxiety [6% vs 0%] as were decreases in bone mineral density measurement; no mention of ALT elevations or hepatotoxicity).

Carr B, Giudice L, Dmowski WP, O'Brien C, Jiang P, Burke J, Jimenez R, et al. Elagolix, an oral GnRH antagonist for endometriosis-associated pain: a randomized controlled study. J Endometr Pelvic Pain Disord 2013; 5: 105-15. PubMed PMID: 30320043.

(Among 137 women with painful endometriosis treated with elagolix or placebo for 8 weeks, reductions in pain scores were greater with elagolix while overall adverse event rates were similar; nausea, headache and hot flushes occurred in 10% of elagolix treated subjects and there were "no clinically meaningful changes in laboratory results").

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to GnRH agonists or antagonists such as elagolix).

Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, Diamond MP, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. N Engl J Med 2017; 377: 28-40. PubMed PMID: 28525302.

(Among 1686 women with endometriosis and moderate-to-severe pain treated with elagolix [150 mg once or 250 mg twice daily] vs placebo for 6 months in two randomized trials, clinical responses occurred in 42% on low and 72% on high dose elagolix vs 23% on placebo, while adverse events that were more frequent with active drug included symptoms of hot flushes, headache and nausea, decreases in bone density and increases in cholesterol; no mention of ALT elevations or hepatotoxicity).

Carr BR, Stewart EA, Archer DF, Al-Hendy A, Bradley L, Watts NB, Diamond MP, et al. Elagolix alone or with add-back therapy in women with heavy menstrual bleeding and uterine leiomyomas: a randomized controlled trial. Obstet Gynecol 2018; 132: 1252-64. PubMed PMID: 30303923.

(Among 567 premenopausal women with heavy menstrual bleeding were treated with elagolix [300 or 600 mg daily] with or without two doses of estrogen/progestin or placebo for 6 months, menstrual bleeding decreased significantly in all groups receiving elagolix while adverse events were more with elagolix, ALT elevations above 3 times ULN occurred in 2% of subjects, but resolved in all and were not accompanied by symptoms or jaundice).

Surrey E, Taylor HS, Giudice L, Lessey BA, Abrao MS, Archer DF, Diamond MP, et al. Long-term outcomes of elagolix in women with endometriosis: results from two extension studies. Obstet Gynecol 2018; 132: 147-60. PubMed PMID: 29889764.

(Among 569 women with painful endometriosis who participated in randomized controlled trials of elagolix [Taylor 2017] who continued on therapy for another 6 months, response rates remained high [52% and 78%] and adverse events were similar; no mention of ALT elevations or hepatotoxicity).

Elagolix (Orilissa)--an oral GnRH antagonist for endometriosis pain. Med Lett Drugs Ther 2018; 60 (1556): 158-60. PubMed PMID: 30383729.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of elagolix vs other treatments for endometriosis pain; mentions that aminotransferase levels rose to above 3 times ULN in 0.2% on 150 mg once daily and 1.1% on 200 mg twice daily).

Lamb YN. Elagolix: first global approval. Drugs 2018; 78: 1501-8. PubMed PMID: 30194661.

(Review of the history of development, mechanism of action, structure, pharmacology, clinical efficacy and side effects of elagolix; mentions that ALT elevations above 3 times ULN occurred in 0.2% on 150 mg daily, 1.1% on 200 mg twice daily and 0.1% of placebo recipients).