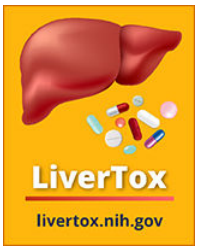
U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Selective Estrogen Receptor Modulators. [Updated 2017 Sep 21].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



Selective Estrogen Receptor Modulators

Updated: September 21, 2017.

OVERVIEW

Introduction

The selective estrogen receptor modulators (SERMs) are a group of nonsteroidal compounds that have estrogen-like effects (agonism) on some tissues (such as bone, skin, heart or vaginal epithelium), but antiestrogen effects (antagonism) on other tissues (such as breast or uterus). Depending on the tissue specificity and balance of the agonist and antagonist activities, these agents have different clinical effects, different indications and different adverse side effects. Typical indications for SERMS include treatment or prevention of breast cancer (tamoxifen, toremifene, raloxifene), treatment or prevention of postmenopausal osteoporosis (raloxifene, bazedoxifene) and amelioration of symptoms of menopause symptoms (ospemifene). Separate documents for the SERMs that are used largely for prevention of cancer, tamoxifen and toremifene, are available in LiverTox. This document summaries background information and the potential hepatotoxicity of raloxifene, bazedoxifene and ospemifene, SERMs used for treatment of nonmalignant conditions such as osteoporosis and menopausal symptoms of hot flashes and dyspareunia.

Drug Class: Antineoplastic Agents, Osteoporosis Agents

Raloxifene

Background

Raloxifene (ral ox' i feen) is a selective estrogen receptor modulator that has estrogen-like effects (agonism) on bone and the cardiovascular system but antiestrogen activity (antagonism) on breast and uterus tissue. This differential activity takes advantage of the beneficial effects of estrogens on bone in decreasing bone resorption and turnover and thus preventing osteoporosis, while avoiding the potential harmful effects of estrogen stimulation of breast and uterine tissue. In several large clinical trials, raloxifene was shown to increase bone mineral density and prevent bone fractures in postmenopausal women at high risk for osteoporosis, while decreasing serum cholesterol levels (both total and LDL) and without stimulating breast and uterine growth. Raloxifene was approved for treatment and prevention of postmenopausal osteoporosis in the United States in 1997, and indications were expanded in 2007 to include reduction of risk of breast cancer in postmenopausal women with osteoporosis as well as those at high risk of breast cancer. Raloxifene is available in tablets of 60 mg generically and under the brand name Evista, and the recommended dose is 60 mg daily. Side effects are not common, but can include hot flashes, leg cramps, peripheral edema, arthralgias and sweating. Rare, but potentially severe adverse events include deep venous thrombosis, pulmonary embolism and ischemic strokes, side effects that it shares with estrogen.

Hepatotoxicity

In large, prelicensure clinical trials, the rate of serum enzyme elevations during raloxifene therapy was less than 1% and was no higher than with placebo or comparator arms. In addition, no episodes of hepatitis or clinically apparent liver injury attributable to raloxifene were reported. In the two decades since its approval and wide scale use, there have been isolated reports of liver injury attributed to raloxifene. One report described a case of cholestatic hepatitis arising a month after starting raloxifene which resolved with stopping, but full recovery was delayed (Case 1). The injury was accompanied by mild immunoallergic features, but autoantibodies were not present. A second case of cholestatic hepatitis was reported in a patient on long term raloxifene who had been started on fenofibrate two weeks before the onset of jaundice. The injury was attributed to the combination of the two agents and possible drug-drug interactions. Finally, several cases of an exacerbation of nonalcoholic steatohepatitis during raloxifene therapy have been reported, a pattern of injury that has been reported more commonly with tamoxifen. Thus, raloxifene may be a rare cause of liver injury, but the relationship to the drug has not been very well established.

Likelihood score: C (probable rare cause of clinically apparent liver injury).

Mechanism of Injury

The reason why raloxifene might cause liver injury is not known, but the isolated cholestatic cases appear to be due to an idiosyncratic hypersensitivity reaction. Raloxifene is metabolized in the liver by glucuronidation and it has minimal effects on cytochrome P450 enzymes (CYP).

Outcome and Management

Serum enzyme elevations are uncommon during raloxifene therapy and are rarely dose limiting. While clinically apparent liver injury with jaundice has been reported with raloxifene therapy, it is very rare. Evaluation should include assessment of hepatic steatosis by ultrasound or other imaging modalities. There is no known cross sensitivity to hepatic injury among the SERMs or with other agents for osteoporosis. On the other hand, restarting raloxifene after clinically apparent liver injury cannot be recommended.

Drug Class: Antineoplastic Agents, Osteoporosis Agents

CASE REPORT

Case 1. Immunoallergic cholestatic hepatitis due to raloxifene.

[Modified from: Vilches AR, Pérez V, Suchecki DE. Raloxifene-associated hepatitis. Lancet 1998; 352 (9139): 1524-5. PubMed Citation]

A 49 year old postmenopausal woman with osteoporosis developed fatigue and rash approximately one month after starting raloxifene and calcium for postmenopausal osteoporosis. She stopped her medications, but 5 days later developed jaundice and sought medical advice. She had no history of liver disease and had normal liver tests before starting raloxifene. On examination, she was jaundiced and had a mild, morbilliform rash. She did not have fever or signs of chronic liver disease. Laboratory tests showed total bilirubin of 6.2 mg/dL, ALT 291 U/L, AST 224 U/L, alkaline phosphatase 643 U/L and slightly elevated eosinophil counts (Table). Tests for hepatitis A, B and C were negative as were routine autoantibodies. Abdominal ultrasound showed no evidence of biliary obstruction or hepatic masses. Serum enzyme levels slowly improved, but bilirubin levels rose to a peak of 15.1 mg/dL. She developed pruritus, but eventually improved with resolution of jaundice and symptoms. Serum alkaline phosphatase levels, however, remained high.

Key Points

Medication:	Raloxifene (60 mg daily)
Pattern:	Cholestatic (R=1.6)
Severity:	3+ (bilirubin elevation, hospitalization)
Latency:	4-5 weeks
Recovery:	Partial at 18 weeks
Other medications:	None mentioned, except for calcium carbonate

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre	Pre	Normal	Normal	Normal	Values not given
5 weeks	5 days	291	643	6.2	Eosinophils 520/μL
2 months	1 month			15.1	Pruritus
5 months	4 months	36	365	1.1	Asymptomatic
Normal Values		**<35**	**<120**	**<1.2**	

Comment

This brief report described a woman with osteoporosis who developed a somewhat prolonged cholestatic hepatitis one month after starting raloxifene. The injury was accompanied by rash and eosinophilia suggestive of an immunoallergic hypersensitivity reaction. She was symptomatic for more than a month, and serum alkaline phosphatase levels were still 3 times the upper limit of normal four months after stopping the drug. Little else besides biliary tract disease could cause this clinical picture, and this report remains the most convincing report of clinically apparent liver injury from raloxifene.

Bazedoxifene

Background

Bazedoxifene (ba" ze dox' i feen) is a selective estrogen receptor modulator that is used to prevent osteoporosis in menopausal women and for treatment of moderate-to-severe vasomotor symptoms associated with menopause (hot flashes, sweating). Bazedoxifene has estrogen-like effects (agonism) on bone and the cardiovascular system, but antiestrogen activity (antagonism) on breast and uterus tissue. This differential activity is keyed to achieving the beneficial effects of estrogens on bone in decreasing bone resorption and turnover and thus preventing osteoporosis, but avoiding the potential harmful effects of estrogen stimulation of breast and uterine tissue. While bazedoxifene by itself is approved for use in several other countries of the world, in the United States it is approved only as a combination product with low doses of conjugated estrogens. In short term trials the combination of bazedoxifene and estrogens was shown to decrease menopause associated hot flushes. Longer term trials of this combination have documented its efficacy in preventing osteoporosis in postmenopausal women. The fixed combination of bazedoxifene (20 mg) and conjugated estrogens (0.45 mg) was approved for use in the United States under the brand name Duavee in 2013. Common side effects include muscle spasms, nausea, diarrhea, dyspepsia, dizziness and abdominal, throat and neck pain. Potential long term, severe adverse events include deep venous thrombosis, pulmonary embolism and ischemic strokes and the possible long term effects of estrogens such as increased risk of breast, endometrial and ovarian cancer and gallbladder disease.

Hepatotoxicity

In large, prelicensure clinical trials, the rate of serum enzyme elevations during combination therapy with bazedoxifene and estrogens was no higher than with placebo or comparator arms, and no episodes of hepatitis or clinically apparent liver injury were reported. Since its approval and more wide spread use, there have been no published reports of clinically apparent liver injury associated with this combination product.

Likelihood score: E* (unlikely cause of clinically apparent liver injury, but suspected to be capable of causing the liver injury reported with other SERMs and estrogens).

Mechanism of Injury

The reason why bazedoxifene might cause liver injury is not known, but its chemical structure is not unlike other SERMs that have been linked to idiosyncratic liver injury. While estrogens can be associated with a cholestatic liver injury arising soon after initiation of treatment, this typical syndrome has not been reported with bazedoxifene combined with conjugated estrogens, perhaps because of the low doses of estrogens used.

Outcome and Management

Serum enzyme elevations are uncommon during bazedoxifene/estrogen therapy and have rarely required dose reduction. While clinically apparent liver injury with jaundice has not been reported with bazedoxifene therapy, it has been reported with other SERMs such as tamoxifen and raloxifene. There is no known cross sensitivity to hepatic injury among the SERMs.

Drug Class: Osteoporosis Agents

Ospemifene

Background

Ospemifene (os pem' i feen) is a selective estrogen receptor modulator that is used for the treatment of moderate-to-severe menopausal symptoms of dyspareunia such as vaginal atrophy, dryness, itching and irritation as well as pain on intercourse. Ospemifene has estrogen-like effects (agonism) on vaginal epithelium, but antiestrogen activity (antagonism) on breast tissue. This differential activity is keyed to achieving the beneficial effects of estrogens on vaginal secretions and epithelial integrity, while avoiding the potential harmful effects of estrogen stimulation of breast tissue. In several large clinical trials, ospemifene was shown to decrease symptoms of dyspareunia (vaginal dryness and discharge and pain on intercourse) without stimulating breast and uterine growth. Ospemifene was approved for treatment of moderate-to-severe symptoms of dyspareunia in postmenopausal women in the United States in 2013. It is not approved for treatment or prevention of osteoporosis. Ospemifene is available in tablets of 60 mg under the brand name Osphena and the recommended dose is 60 mg daily. Long term therapy is not recommended. Side effects are not common, but can include hot flashes, muscle spasms, vaginal discharge and sweating. Rare, but potentially severe long term adverse events include deep venous thrombosis, pulmonary embolism and ischemic strokes.

Hepatotoxicity

In large, prelicensure clinical trials, the rate of serum enzyme elevations during ospemifene therapy was no higher than with placebo or comparator arms. In addition, no episodes of hepatitis or clinically apparent liver injury were reported in these studies. While ospemifene has had only limited widescale use, it has not been linked to episodes of liver injury in the published literature or to the cholestatic hepatitis that has been linked to other SERMs such as tamoxifen and raloxifene.

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

Mechanism of Injury

The reason why ospemifene might cause liver injury is not known, but isolated idiosyncratic cases of cholestatic hepatitis have been linked to therapy with other SERMs. Ospemifene is metabolized in the liver by glucuronidation and has minimal effects on cytochrome P450 (CYP) enzyme activity.

Outcome and Management

Serum enzyme elevations are uncommon during ospemifene therapy and are rarely dose limiting. There is no known cross sensitivity to hepatic injury among the SERMs.

Drug Class: Hormonal Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Raloxifene – Generic, Evista®

Bazedoxifene with Conjugated Estrogens – Duavee®

Ospemifene – Osphena®

DRUG CLASS

(Raloxifene) Antineoplastic Agents; Osteoporosis Agents

(Bazedoxifene) Osteoporosis Agents

(Ospemifene) Hormonal Agents

COMPLETE LABELING

(Raloxifene) Product labeling at DailyMed, National Library of Medicine, NIH

COMPLETE LABELING

(Bazedoxifene) Product labeling at DailyMed, National Library of Medicine, NIH

COMPLETE LABELING

(Ospemifene) Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

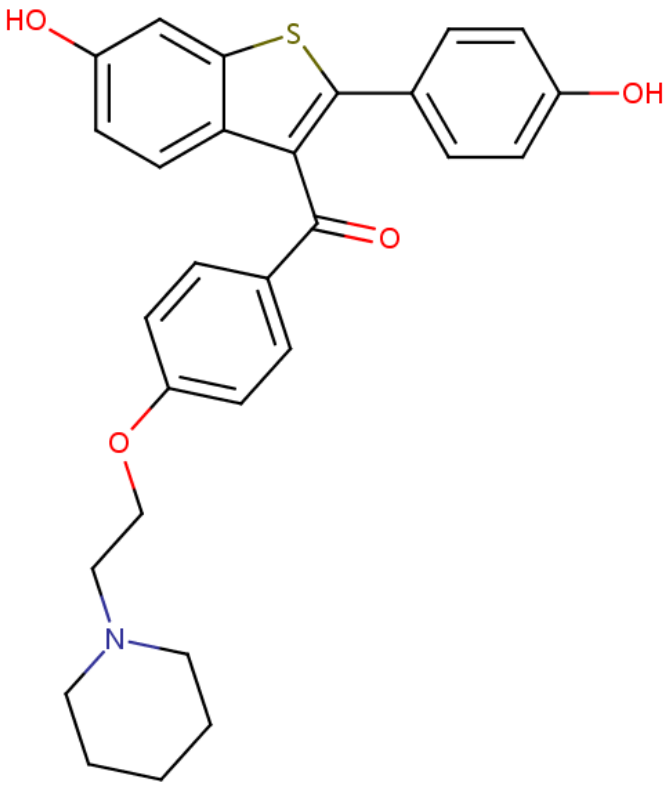
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Raloxifene	84449-90-1	C28-H27-N-O4-S	

Table continued from previous page.

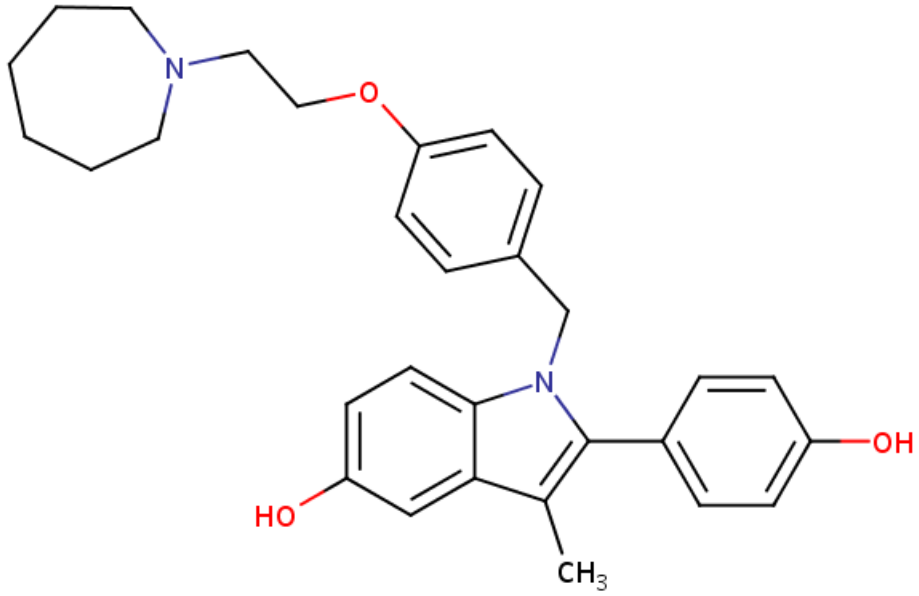
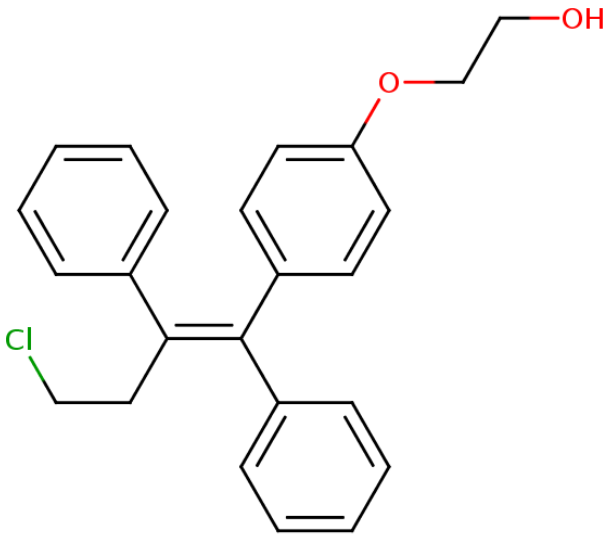
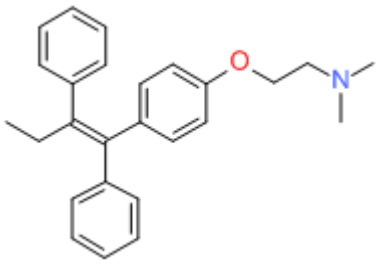
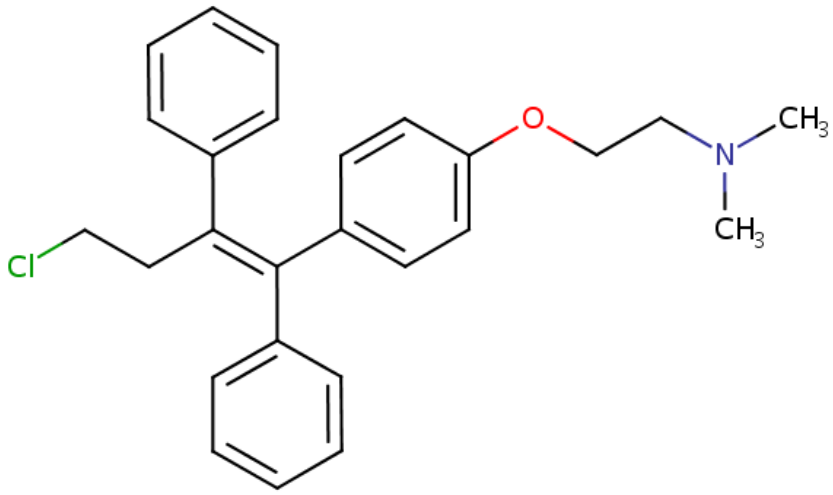
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Bazedoxifene	198481-32-2	C6-H13-N-O5	
Ospemifene	128607-22-7	Unspecified	

Table continued from previous page.

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Tamoxifen	10540-29-1	C26-H29-N-O	
Toremifene	89778-26-7	C26-H28-Cl-N-O	

ANNOTATED BIBLIOGRAPHY

References updated: 21 September 2017

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 mentions that tamoxifen can lead to cholestasis, peliosis hepatis, fatty liver, steatohepatitis and cirrhosis, and that raloxifene was implicated in at least one case of hepatotoxicity).

Chitturi S, Farrell GC. Estrogen receptor antagonists. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 610-2.

(Review of hepatotoxicity of estrogen receptor antagonists discusses tamoxifen and toremifene, but not raloxifene, bazedoxifene or ospemifene).

Moy B, Lee RJ, Smith M. Anti-estrogen therapy. Natural products in cancer chemotherapy. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1756-9.

(Textbook of pharmacology and therapeutics).

Raloxifene for postmenopausal osteoporosis. Med Lett Drugs Ther 1998; 40 (1022): 29-30. PubMed PMID: 9529516.

(Concise summary of the mechanism of action, clinical efficacy, safety, drug interactions and costs of raloxifene shortly after its approval in the United States for postmenopausal osteoporosis, mentions side effects of hot flashes and leg cramps and the risk of venous thrombosis and fetal abnormalities; no mention of ALT elevations or hepatotoxicity).

Toremifene and letrozole for advanced breast cancer. Med Lett Drugs Ther 1998; 40 (1024): 43-5. PubMed PMID: 9580744.

(Concise summary of the clinical efficacy and side effects of toremifene and letrozole shortly after their approval in the United States as therapies for invasive breast cancer, mentions that side effects of toremifene are similar to those of tamoxifen and that ALT elevations can occur).

Vilches AR, Pérez V, Suchecki DE. Raloxifene-associated hepatitis. Lancet 1998; 352 (9139): 1524-5. PubMed PMID: 9820309.

(49 year old woman with osteoporosis developed cholestatic hepatitis 1 month after starting raloxifene [bilirubin 6.2 mg/dL, ALT 2913 U/L, Alk P 643 U/L, mild eosinophilia], resolving slowly and incompletely by four months after stopping: Case 1).

Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999; 281: 2189-97. PubMed PMID: 10376571.

(Among 7705 postmenopausal women with osteoporosis treated with raloxifene [60 or 120 mg] or placebo daily for 3 years, raloxifene decreased the risk of invasive breast cancer, but increased the risk of venous thrombosis, and side effects included hot flushes, leg cramps and venous thrombosis; no mention of ALT elevations or hepatotoxicity).

Hamada N, Ogawa Y, Saibara T, Murata Y, Kariya S, Nishioka A, Terashima M, et al. Toremifene-induced fatty liver and NASH in breast cancer patients with breast-conservation treatment. Int J Oncol 2000; 17: 1119-23. PubMed PMID: 11078796.

(Among 52 women with breast cancer treated with toremifene for 3 to 5 years, 4 [8%] developed fatty liver disease by CT scan, 2 with raised ALT and AST levels and one with steatohepatitis on liver biopsy).

Drugs for prevention and treatment of postmenopausal osteoporosis. Med Lett Drugs Ther 2000; 42 (1090): 97-100. PubMed PMID: 11035622.

(Concise summary of the clinical efficacy and adverse effects of drugs for postmenopausal osteoporosis, including raloxifene and bazedoxifene with conjugated estrogens).

Martino S, Cauley JA, Barrett-Connor E, Powles TJ, Mershon J, Disch D, Secrest RJ, et al.; CORE Investigators. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst 2004; 96: 1751-61. PubMed PMID: 15572757.

(Among 4011 women with high risk of breast cancer treated with raloxifene or placebo for up to 8 years, total as well as serious adverse events and discontinuations because of adverse events were similar in the two groups; no mention of ALT elevations or hepatotoxicity).

Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, McNabb MA, et al.; Raloxifene Use for The Heart (RUTH) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006; 355: 125-37. PubMed PMID: 16837676.

(Among 10,101 postmenopausal women with risk factors of coronary artery disease treated with raloxifene or placebo for an average of 5.6 years, coronary artery events were similar in both groups, but breast cancer rates were lower with raloxifene; adverse events included hot flushes [8% vs 5%], leg cramps [10% vs 7%], peripheral edema [14% vs 12%] and gall bladder disease [5.6% vs 4.5%]; no mention of ALT elevations or hepatotoxicity).

Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, Bevers TB, et al.; National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 2006; 295: 2727-41. PubMed PMID: 16754727.

(Among 19,747 postmenopausal women with high risk for breast cancer treated with either tamoxifen [20 mg daily] or raloxifene [60 mg daily] for an average of 5 years, invasive breast and uterine cancer rates were similar as were numbers of osteoporotic fractures; no mention of ALT elevations or clinically apparent liver disease).

Raloxifene (Evista) for breast cancer prevention in postmenopausal women. Med Lett Drugs Ther 2006; 48 (1234): 37. PubMed PMID: 16685245.

(Concise summary of the clinical efficacy, safety and costs of raloxifene shortly after its approval in the United States for prevention of breast cancer, mentions that venous thromboses were lower with raloxifene than tamoxifen; no mention of ALT elevations or hepatotoxicity).

Lucena MI, Andrade RJ, Vicioso L, González FJ, Pachkoria K, García-Muñoz B. Prolonged cholestasis after raloxifene and fenofibrate interaction: A case report. World J Gastroenterol 2006; 12: 5244-6. PubMed PMID: 16937543.

(60 year old woman with osteoporosis developed jaundice two weeks after starting fenofibrate and while on chronic raloxifene therapy [bilirubin 11.1 rising to 21.8 mg/dL, ALT 241 U/L, Alk P 174 U/L], resolving slowly and incompletely with persistent Alk P elevations two years later [bilirubin 0.8 mg/dL, ALT 60 U/L, Alk P 444 U/L]).

Takamura T, Shimizu A, Komura T, Ando H, Zen Y, Minato H, Matsushita E, Kaneko S. Selective estrogen receptor modulator raloxifene-associated aggravation of nonalcoholic steatohepatitis. Intern Med 2007; 46: 579-81. PubMed PMID: 17473493.

(53 year old woman with postmenopausal osteoporosis and mild serum enzyme elevations attributed to fatty liver disease developed more marked enzyme elevations within a few months of starting raloxifene [bilirubin not given, ALT rising from 82 to 356 U/L, Alk P from 199 to 414 U/L] despite little weight gain, biopsy showing bridging fibrosis and steatohepatitis and values falling to baseline after stopping raloxifene).

Miller PD, Chines AA, Christiansen C, Hoeck HC, Kendler DL, Lewiecki EM, Woodson G, et al. Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. J Bone Miner Res 2008; 23: 525-35. PubMed PMID: 18072873.

(Among 1434 postmenopausal women with osteoporosis treated with 3 doses of bazedoxifene [10, 20 or 40 mg] or placebo daily for 2 years, adverse events usually attributed to bazedoxifene included hot flushes [20-24% vs 14%], leg cramps [9-12% vs 11.6%] and venous thrombosis [0.0-0.6% vs 0.3%); no mention of ALT elevations or hepatotoxicity or deaths from liver disease).

Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ, Constantine GD, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with

osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res 2008; 23: 1923-34. PubMed PMID: 18665787.

(Among 6847 postmenopausal women with osteoporosis treated for 3 years, new vertebral fractures were less with bazedoxifene and raloxifene compared to placebo, but hot flushes, leg cramps and venous thromboses were more frequent; no mention of ALT elevations or clinically apparent liver injury).

Pinkerton JV, Utian WH, Constantine GD, Olivier S, Pickar JH. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/ conjugated estrogens: a randomized, controlled trial. Menopause 2009; 16: 1116-24. PubMed PMID: 19546826.

(Among 332 postmenopausal women with hot flushes treated with bazedoxifene/estrogens or placebo for 12 weeks, hot flushes decreased with active therapy by 74-80% and with placebo by 54%; adverse event rates were similar in the all groups; no mention of ALT levels or hepatotoxicity).

Bachmann GA, Komi JO; Ospemifene Study Group. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause 2010; 17: 480-6. PubMed PMID: 20032798.

(Among 826 postmenopausal women with vulvo-vaginal atrophy treated with ospemifene [30 or 60 mg] or placebo daily for 12 weeks, symptoms of vaginal dryness and dyspareunia improved most with the higher dose of ospemifene, and adverse events were similar in the three groups except for hot flushes [9.6% and 8.3% vs 3.4%] and "all laboratory and safety parameters remained at essentially the same levels throughout the study").

Matsumura M, Tashiro K, Miura A, Tajima T, Kinoshita I, Kojima E, Yoshizawa A. [A case of non-alcoholic fatty liver disease (NAFLD) aggravated after treatment with raloxifene]. Nihon Shokakibyo Gakkai Zasshi 2011; 108 (12): 2036-41. Japanese. PubMed PMID: 22139492.

(70 year old woman with osteoporosis and nonalcoholic fatty liver developed worsening liver test abnormalities within 3 months of starting raloxifene [bilirubin 0.4 mg/dL, ALT rising from 30-50 to 154 U/L, Alk P 422 U/L], biopsy showing NASH and fibrosis, ALT improving upon stopping raloxifene and starting ursodiol).

Silverman SL, Chines AA, Kendler DL, Kung AW, Teglbjærg CS, Felsenberg D, Mairon N, et al.; Bazedoxifene Study Group. Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled study. Osteoporos Int 2012; 23: 351-63. PubMed PMID: 21779819.

(In a 2 year extension of a 3 year study of 2 doses of bazedoxifene vs placebo in 4216 postmenopausal women with osteoporosis, adverse events were similar in the 3 groups except for hot flushes, leg cramps and deep venous thrombosis [0.5% and 0.6% vs 0.2%]; no mention of ALT elevations or hepatotoxicity).

Palacios S, de Villiers TJ, Nardone Fde C, Levine AB, Williams R, Hines T, Mirkin S, et al.; BZA Study Group. Assessment of the safety of long-term bazedoxifene treatment on the reproductive tract in postmenopausal women with osteoporosis: results of a 7-year, randomized, placebo-controlled, phase 3 study. Maturitas 2013; 76: 81-7. PubMed PMID: 23871271.

(Among 1301 women with osteoporosis treated with bazedoxifene or placebo for up to 7 years, serious adverse events and breast, endometrial and ovarian complications were similar in the two groups; no mention of ALT elevations or clinically apparent liver injury).

Simon JA, Lin VH, Radovich C, Bachmann GA; Ospemifene Study Group. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause 2013; 20: 418-27. PubMed PMID: 23096251.

(Among 180 postmenopausal women with vulvar and vaginal atrophy treated with ospemifene or placebo for up to one year, side effects more common with ospemifene included hot flashes and vaginal candidiasis or mycotic infections; no mention of ALT elevations or clinically apparent liver injury).

Ospemifene (Osphena) for dyspareunia. Med Lett Drugs Ther 2013; 55 (1420): 55-6. PubMed PMID: 23836373.

(Concise summary of the mechanism of action, clinical efficacy, safety, drug interactions and costs of ospemifene shortly after its approval in the US for postmenopausal dyspareunia, mentions side effects of hot flashes, vaginal discharge, muscle spasms and sweating; no mention of ALT elevations or hepatotoxicity).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25,1425. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none of the 96 were attributed to a selective estrogen receptor modulator).

Pinkerton JV, Harvey JA, Lindsay R, Pan K, Chines AA, Mirkin S, Archer DF; SMART-5 Investigators. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab 2014; 99: E189-98. PubMed PMID: 24438370.

(Among 1843 postmenopausal women receiving bazedoxifene/estrogens, bazedoxifene alone, estrogens/progesterone or placebo for at least 12 months, bone density improved with bazedoxifene and estrogens, but not placebo treatment and side effects were less with bazedoxifene with estrogens than with estrogens with progestins; no mention of ALT elevations or hepatotoxicity).

Conjugated estrogens/bazedoxifene (Duavee) for menopausal symptoms and prevention of osteoporosis. Med Lett Drugs Ther 2014; 56 (1441): 33-4. PubMed PMID: 24759293.

(Concise summary of the mechanism of action, clinical efficacy, safety and costs of estrogens, bazedoxifene and the combination of the two shortly after approval of the combination in the United States for prevention of postmenopausal osteoporosis, mentions that side effects are similar to those with placebo; no mention of ALT elevations or hepatotoxicity).

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 in the US collected between 2004 and 2012, 4 cases were attributed to tamoxifen but none were attributed to raloxifene, toremifene or other selective estrogen receptor modulators).

Ellis AJ, Hendrick VM, Williams R, Komm BS. Selective estrogen receptor modulators in clinical practice: a safety overview. Expert Opin Drug Saf 2015; 14: 921-34. PubMed PMID: 25936229.

(Review of the safety of SERMs focusing upon breast, uterine and cardiovascular adverse events; no mention of ALT elevations or liver disease).