New Options and Controversies for "Women's Problems": 51st Annual McGill Course In Drug Therapy

CLEVE ZIEGLER, M.D., FRCS
JEWISH GENERAL HOSPITAL

Objectives:

- 1. Evolving trends in contraception
- 2. New treatment options for benign gynecological conditions
- 3. New treatment paradigm for menopause

Contraception in Canada

Canadian Contraceptive Landscape

15% never use contraception[1]

20% have difficulties with contraceptive adherence[1]

40% of all pregnancies in Canada are unintended[2]

1. Black A et al. *J Obstet Gynaecol Can* 2009;31:627-40; 2. Black AY et al. *J Obstet Gynaecol Can* 2015;37:1086-97.

3

LARCs: Long-acting Reversible Contraceptives

Canadian Contraceptive Landscape

What are LARCs?

- Reversible contraceptives that require administration less than once per year[1]
- Include subdermal hormonal implants and intrauterine contraceptives (copper or levonorgestrel IUCs)[1]

IUC, intrauterine contraceptive; LARC, long-actiing reversible contraceptives
1. Hauck B, Costescu D. *J Obstet Gynaecol Can* 2015; 37:606-16.

4

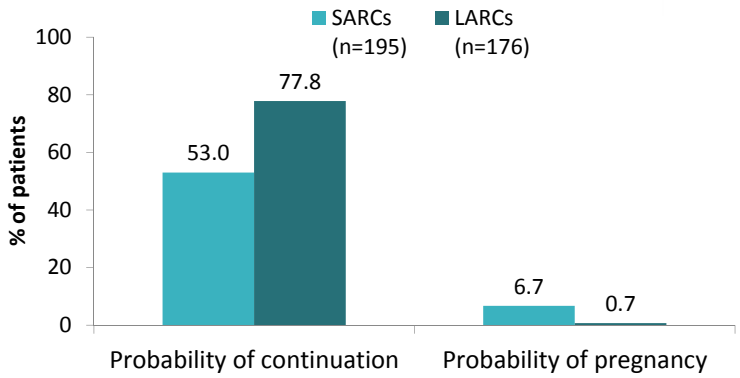
LARCs Compared with Short-acting Contraceptives

Canadian Contraceptive Landscape

Randomized study of US women (18 to 29 years) at 12 months of contraceptive use[2]*

KEY TAKEAWAY

LARCs result in fewer unintended pregnancies and are more likely to be continued than short-acting options



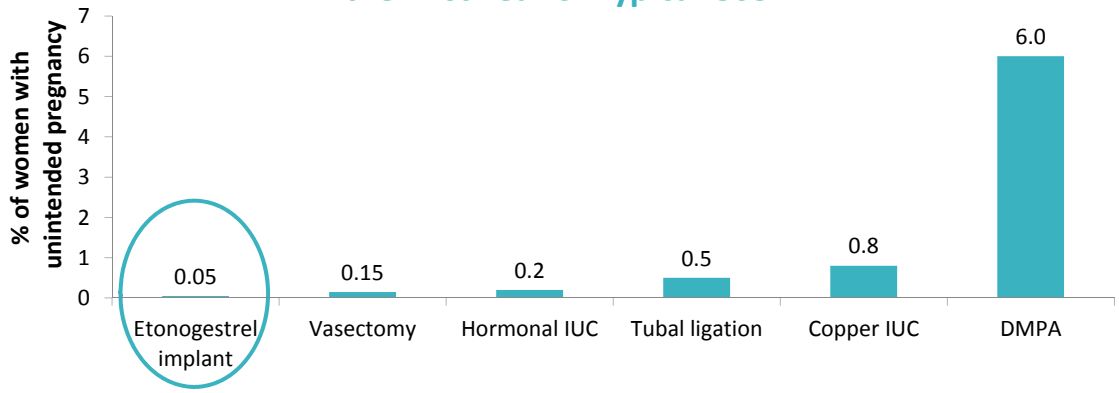
SARCs included oral contraceptives and depot medroxyprogesterone acetate; LARCs included intrauterine contraceptives and implants
LARC, long-actiing reversible contraceptives; SARC, short-acting reversible contraceptives
Hubacher D et al. *Am J Obstet Gynecol* 2017;216:101-9.

5

Comparative Effectiveness of Long-Term Contraceptives

Mechanism of Action, Pharmacokinetics, and Efficacy

Percentage of Women with Unintended Pregnancy Within the First Year of Typical Use



DMPA, depot medroxyprogesterone acetate; IUC, intrauterine contraceptive
Black AY et al. *J Obstet Gynaecol Can* 2015;37:936-42.

6

Canadian Position Statements on LARCs

Canadian Contraceptive Landscape

THE SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA

Canadian Paediatric Society

Canadian Contraception Consensus

"LARCs are the **most effective method of reversible contraception**, have high continuation rates, and should be considered when presenting contraceptive options to any woman of reproductive age."[1]

Contraceptive care for Canadian Youth

"This statement recommends using **LARCs as first-line contraception for Canadian youth**….[These methods] have the lowest failure rate and are first-tier options."[2]

LARCs, long-acting reversible contraceptives

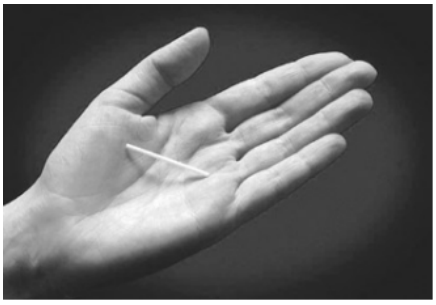
Black A et al. *J Obstet Gynaecol Can* 2015;37:936-42; 2. Di Meglio G et al. *Paediatr Child Health* 2018;23:271-7.

7

Etonogestrel Subdermal Implant: What Is It?

Mechanism of Action, Pharmacokinetics, and Efficacy

- Subdermal, single rod
  - 4 cm long, 2 mm wide
- Effective for up to 3 years
- Progestin-only implant preloaded in a sterile disposable applicator
  - Etonogestrel is the active metabolite of desogestrel, a progestin used in oral contraceptives
- Radiopaque
  - Can be localized by X-ray, computer tomography, ultrasound, or magnetic resonance imaging



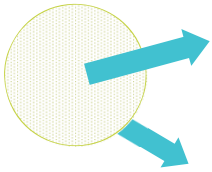
Nexplanon (etonogestrel extended release subdermal implant) product monograph. Kirkland, QC: Merck Canada Inc; 2020; Rowlands S, Searle S. *Open Access Journal of Contraception* 2014;5:73-84.

8

Etonogestrel Subdermal Implant: Components

Components and Insertion Site

Implant



Core:
- **EVA flexible copolymer (non-latex, BPA free)**
- **Barium sulfate (15 mg)**
- **Magnesium stearate (0.1 mg)**

Rate-controlling membrane (implant skin): 100% EVA

Applicator

- **Preloaded, sterile applicator**
- **Single use and disposable**

BPA, bisphenol A; EVA, ethylene vinyl acetate

Nexplanon (etonogestrel extended release subdermal implant) product monograph. Kirkland, QC: Merck Canada Inc; 2020.

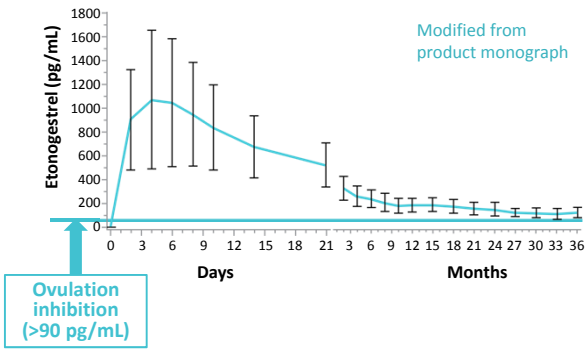
9

Pharmacokinetics Over Time

Mechanism of Action, Pharmacokinetics, and Efficacy

- After reaching peak levels, etonogestrel levels decrease **gradually** over time[1]
- After **implant removal**, etonogestrel levels drop **rapidly**
  - Undetectable levels within 1 week[1]
  - Pregnancies have occurred as soon as 7 to 14 days after removal[1]
  - **Ovulation resumes within 2 to 4 weeks for most women[2]**
- Women should re-start contraception immediately after implant removal if they do not wish to become pregnant[1]

Etonogestrel Serum Concentrations* Over Time After Implant Insertion[1]



Mean levels in pg/mL; bars show standard deviation

1. Nexplanon (etonogestrel extended release subdermal implant) product monograph. Kirkland, QC: Merck Canada Inc; 2020. 2. Palomba S et al. *Gynecol Endocrinol* 2012;28:710-21.

10

Bleeding Patterns Overview

Key Counselling Topics: Bleeding, Dysmenorrhea, and Weight Gain

- Women using hormonal contraceptives may experience changes in bleeding

Etonogestrel subdermal implant bleeding patterns during the first 2 years of use*

Bleeding pattern	Definition	% of 90-day intervals with this pattern
Amenorrhea	No bleeding or spotting	22.2%
Infrequent	<3 bleeding/spotting episodes in 90 days (excluding amenorrhea)	33.6%
Frequent	More than 5 bleeding/spotting episodes	6.7%
Prolonged	Any bleeding/spotting episode > 14 days	17.7%

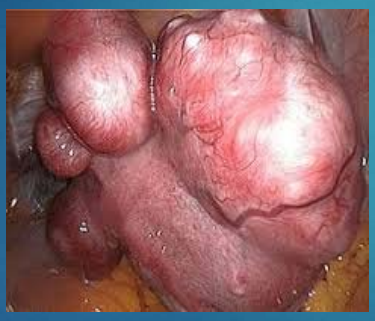
Over half of women have no bleeding or infrequent bleeding

*Based on 3315 recording periods of 90 days duration in 780 women, excluding the first 90 days after implant insertion
Nexplanon (etonogestrel extended release subdermal implant) product monograph. Kirkland, QC: Merck Canada Inc; 2020.

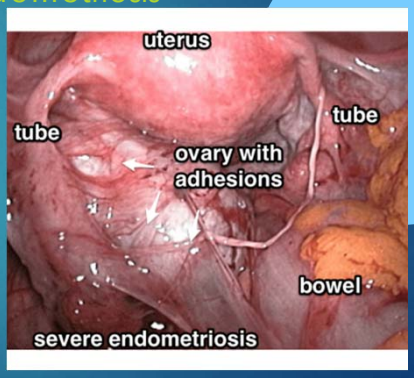
11

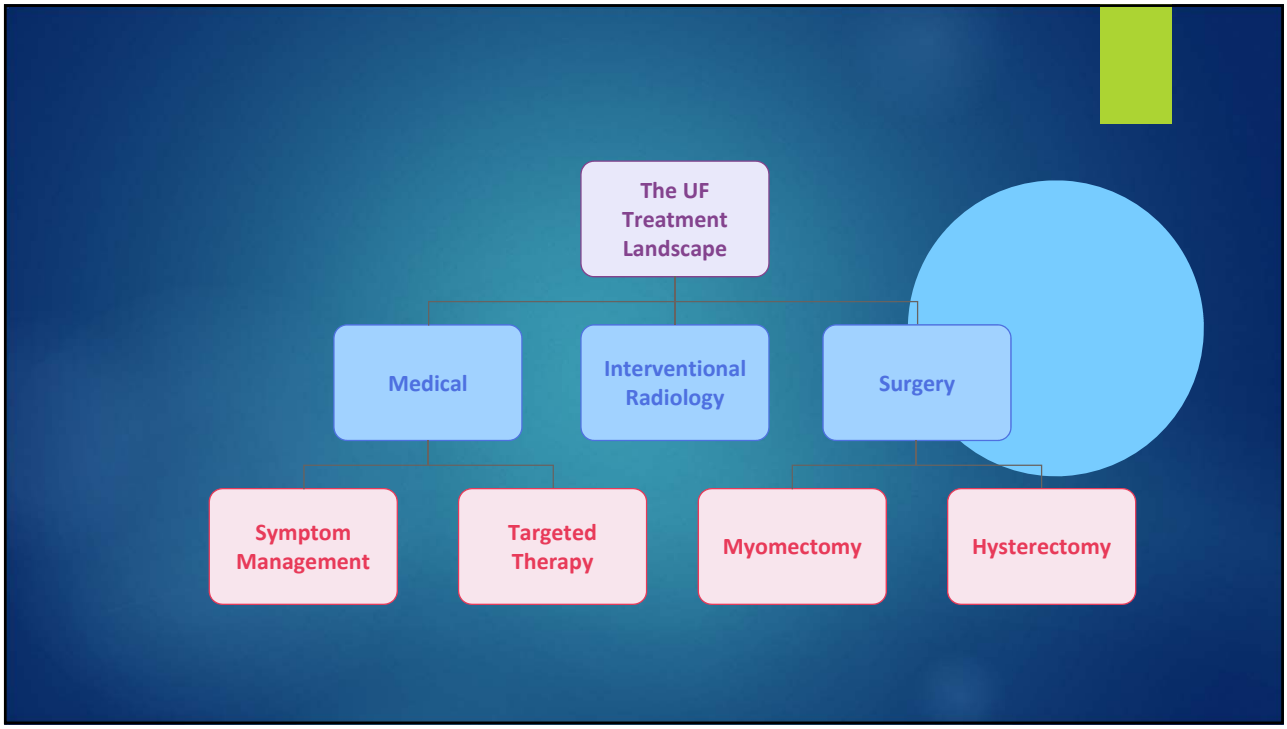
Uterine Fibroids and Endometriosis

Fibroids



Endometriosis

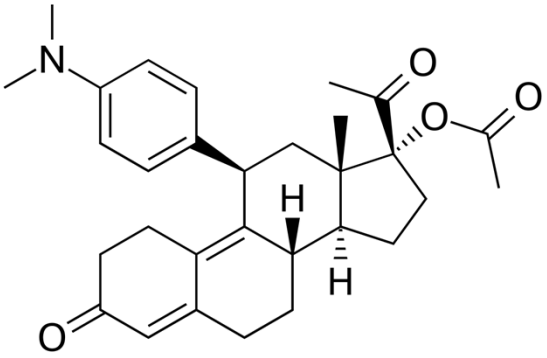




Uterine Fibroids

- Medical Management:
  - Tranexamic Acid
  - Hormonal Contraceptives
  - LNG IUS
  - Ulipristal Acetate
  - GnRH Agonists
  - **GnRH Antagonists**
- Surgical Management:
  - Uterine Preserving (Myomectomy)
    - Hysteroscopic
    - Laparoscopic
    - Open
    - Uterine Artery Embolization
    - **New Options**
  - Hysterectomy

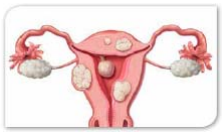
Fibristal



SPRMs Modulate Progesterone Effect Primarily by Targeting Fibroids, Endometrium and the Pituitary

SPRM

Fibroids



Direct action on **fibroids**, reducing their size through the inhibition of cell proliferation and induction of apoptosis

Endometrium

Direct effect on the **endometrium** and stops uterine bleeding. Benign and reversible changes in the endometrial tissue termed "Progesterone Receptor Modulator Associated Endometrial Changes" (PAEC)

Pituitary

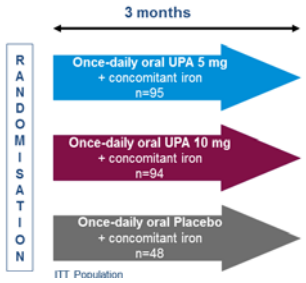
Direct action on the **pituitary**, inducing amenorrhea by inhibiting ovulation and maintaining mid-follicular phase levels of estradiol

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ulipristal Acetate versus Placebo for Fibroid Treatment before Surgery

Jacques Donnez, M.D., Ph.D., Tetyana F. Tatarchuk, M.D., Ph.D., Philippe Bouchard, M.D., Lucian Puscasiu, M.D., Ph.D., Nataliya F. Zakharenko, M.D., Ph.D., Tatiana Ivanova, M.D., Ph.D., Gyula Ugocsai, M.D., Ph.D., Michal Mara, M.D., Ph.D., Manju P. Jilla, M.B., B.S., M.D., Elke Bestel, M.D., Paul Terrill, Ph.D., Ian Osterloh, M.R.C.P., and Ernest Loumaye, M.D., Ph.D., for the PEARL I Study Group*

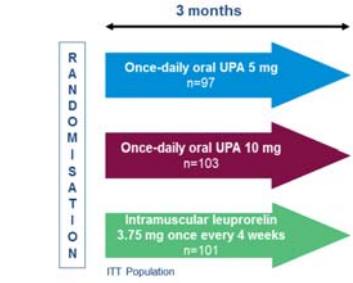


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ulipristal Acetate versus Leuprolide Acetate for Uterine Fibroids

Jacques Donnez, M.D., Ph.D., Janusz Tomaszewski, M.D., Ph.D., Francisco Vázquez, M.D., Ph.D., Philippe Bouchard, M.D., Boguslav Lemieszczuk, M.D., Francesco Baró, M.D., Ph.D., Kazem Nouri, M.D., Luigi Selvaggi, M.D., Krzysztof Sodowski, M.D., Elke Bestel, M.D., Paul Terrill, Ph.D., Ian Osterloh, M.R.C.P., and Ernest Loumaye, M.D., Ph.D., for the PEARL II Study Group*

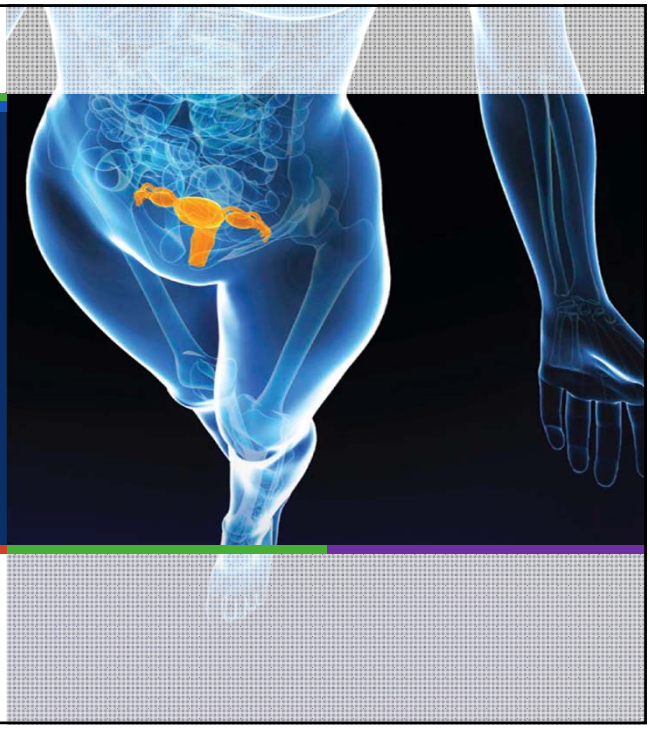


N ENGL J MED 366;5 NEJM.ORG FEBRUARY 2, 2012

Effects of UPA on bleeding control

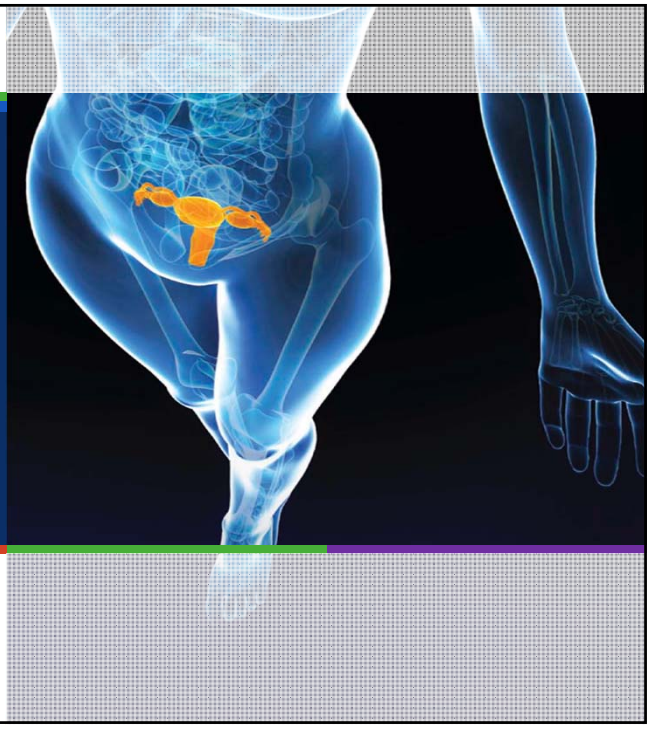
UPA: ulipristal acetate

Effects of UPA on fibroid volume reduction



UPA, ulipristal acetate

Effects of UPA on pain and quality of life



UPA, ulipristal acetate

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 September 2020
EMA/455818/2020

PRAC recommends revoking marketing authorisation of ulipristal acetate for uterine fibroids

A review by EMA's safety committee (PRAC) has confirmed that 5-mg ulipristal acetate (Esmya and generic medicines) used for the treatment of symptoms of uterine fibroids can cause liver injury, including the need for liver transplantation. The PRAC has therefore recommended the revocation of the marketing authorisations of these medicines.

The PRAC considered all the available evidence in its review, including reported cases of serious liver injury. Patient and healthcare professional representatives, including experts in gynaecology, were also consulted. Since it was not possible to identify which patients were most at risk or measures that could reduce the risk, the PRAC concluded that the risks of these medicines outweighed their benefits and that they should not be marketed in the EU.

The use of 5-mg ulipristal acetate medicines for uterine fibroids had already been suspended as a precautionary measure while awaiting the outcome of this review.

Ulipristal acetate is also authorised as a single-dose medicine for emergency contraception. This recommendation does not affect the single-dose ulipristal acetate emergency contraceptive (ellaOne and other trade names) and there is no concern about liver injury with these medicines.

The PRAC recommendation will now be forwarded to EMA's human medicines committee (CHMP), which will adopt the Agency's opinion.

Important Safety Information
FIBRISTAL (ulipristal acetate tablets, 5 mg)
Voluntary Withdrawal in Canada due to Risk of Drug-Induced Liver Injury

Allergan

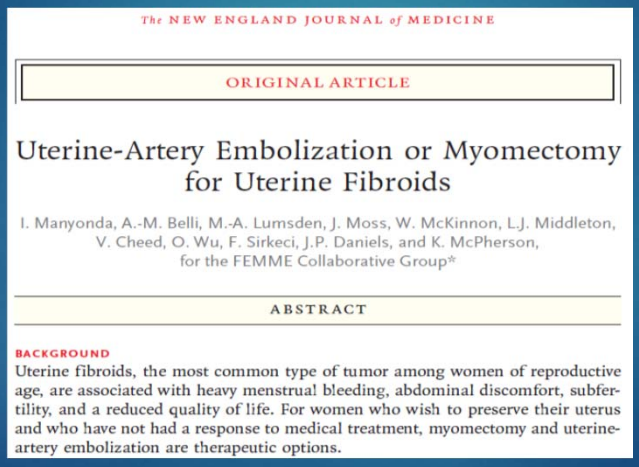
2020/09/30

Audience
Healthcare professionals including obstetricians, gynecologists, primary care physicians with interest in women's health, hepatologists, emergency room physicians, and pharmacists.

Key messages

- **Following rare international cases of severe liver injury requiring liver transplantation, the manufacturer of FIBRISTAL, Allergan Inc., is voluntarily withdrawing the product from the Canadian market. FIBRISTAL was approved in Canada to treat signs and symptoms of uterine fibroids in women of reproductive age.**
- **On September 24, 2020, Allergan Inc. initiated the recall of FIBRISTAL from the Canadian market to the retail pharmacy level.**
- **Healthcare professionals are advised to:**
  - **not prescribe or dispense FIBRISTAL**
  - **contact patients under their care who are currently being treated with FIBRISTAL to stop treatment, and review alternative treatment options**
  - **advise patients who have been taking FIBRISTAL to immediately contact a healthcare professional if they experience signs and symptoms of liver injury such as nausea, vomiting, stomach ache, severe tiredness, yellowing of the eyes or skin, or dark urine, which could occur after stopping treatment**
  - **perform liver function monitoring within 2-4 weeks after treatment with FIBRISTAL has stopped and investigate further if liver function is abnormal**

Uterus Conserving Options



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Uterine-Artery Embolization or Myomectomy for Uterine Fibroids

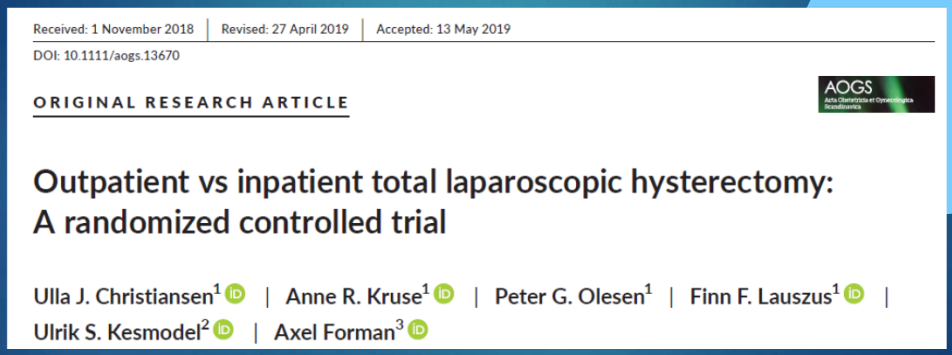
I. Manyonda, A.-M. Belli, M.-A. Lumsden, J. Moss, W. McKinnon, L.J. Middleton, V. Cheed, O. Wu, F. Sirkeci, J.P. Daniels, and K. McPherson, for the FEMME Collaborative Group*

ABSTRACT

BACKGROUND

Uterine fibroids, the most common type of tumor among women of reproductive age, are associated with heavy menstrual bleeding, abdominal discomfort, subfertility, and a reduced quality of life. For women who wish to preserve their uterus and who have not had a response to medical treatment, myomectomy and uterine-artery embolization are therapeutic options.

Making Hysterectomy Safer



Received: 1 November 2018 | Revised: 27 April 2019 | Accepted: 13 May 2019

DOI: 10.1111/aogs.13670

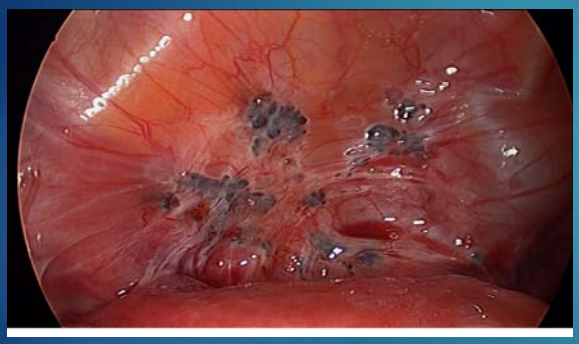
ORIGINAL RESEARCH ARTICLE

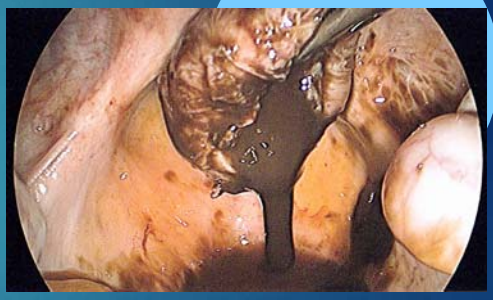
AOGS

Outpatient vs inpatient total laparoscopic hysterectomy: A randomized controlled trial

Ulla J. Christiansen[1] | Anne R. Kruse[1] | Peter G. Olesen[1] | Finn F. Lauszus[1] | Ulrik S. Kesmodel[2] | Axel Forman[3]

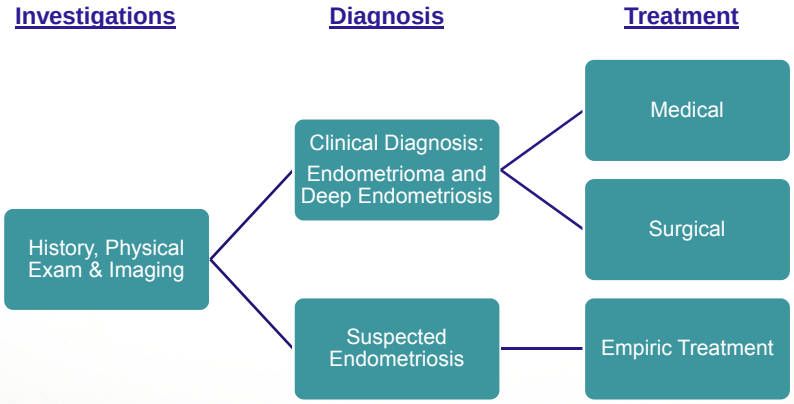
Endometriosis





Non-surgical Diagnosis of "Endometriotic Disease" Is Possible

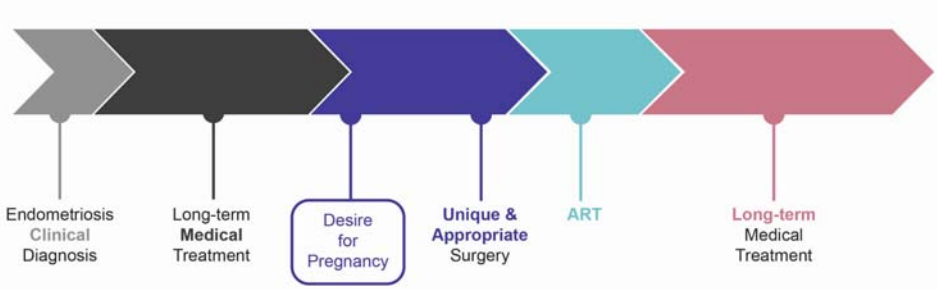
Clinical vs. Suspected Diagnosis of Endometriosis



Bazot M & Darai E. Fertil Steril 2017; 108(6): 886-894. Vercellini P et al. J Obstet Gynaecol Can. 2018; 40(6):726-49

A Proposed Treatment Paradigm

''Endometriosis Life"



ART, assisted reproductive technology.
Chapron, (2018)

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Treatment Options

- Combined Hormonal Contraceptives (CHC)
- GnRH agonists
- Progestins
- GnRH receptor antagonists
- Androgen therapy
- Surgery

GnRH: gonadotrophin releasing hormone

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Treatment Algorithm for Endometriosis-Associated Pain

CHC therapy, continuous or cyclic
Progestins (oral, IUS, depot)
Analgesics (non-opioid)

**pain may persist due to incomplete response or intolerance to first line therapy*

Persistent Pain*

Medical therapies
(GnRH agonists with addback, GnRH receptor antagonists)

Laparoscopy for diagnosis and treatment

Consider multi-modal and interdisciplinary approach for chronic pain

Consider additional imaging, consultation and evaluation for comorbid conditions

CHC: combined hormonal contraceptive; GnRH: gonadotrophin releasing hormone;
IUS: intrauterine system; Adapted from ESHRE, UK NICE guidelines for endometriosis, WES Consensus, SOGC

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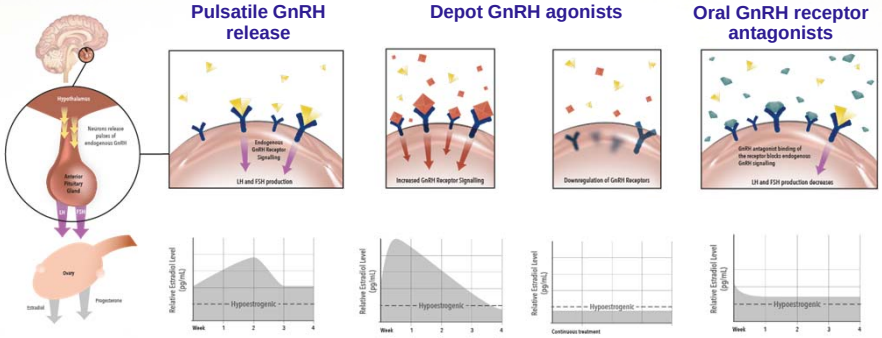
GnRH Agonists vs. Oral GnRH Receptor Antagonists: Mechanisms of Action



Physiological changes in estradiol

- Sustained stimulation causes initial flare
- Continuous exposure leads to desensitization of GnRH receptors and profound inhibition of the HPO axis

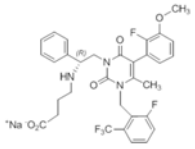
Competitive GnRH receptor antagonists allow dose-dependent suppression of HPO axis

GnRH: gonadotropin-releasing hormone; HPO: hypothalamic-pituitary- ovarian.
1. Nussey S, Whitehead S. Endocrinology: An Integrated Approach. Oxford: BIOS Scientific Publishers. London, UK; 2001. https://www.ncbi.nlm.nih.gov/books/NBK29/?report=printable. Accessed October 9, 2017. 2. Knobil E. Endocrinology 1992; 131:1005-1006. 3. Reed BG, Carr BR. In: De Groot LJ et al, eds. NCBI Bookshelf. Endotext. South Dartmouth, MA; updated May 2015. Accessed November 2, 2017. 4. Zito G et al. Biomed Res Int 2014; 2014:191967. 5. Gordon K et al. J Clin Endocrinol Metab 1991; 73:1262-1268.

30

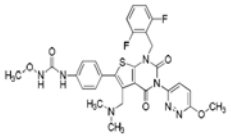
GnRH Receptor Antagonists in Development

ELAGOLIX[1]



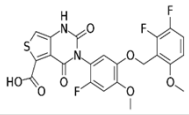
- The only drug approved in the US as Oriahnn for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women
- Phase 3 development in uterine fibroids
  - **300 mg BID with or without E_2/NETA***

RELUGOLIX[2]



- Approved as Relumina (Japan) for the management of symptomatic uterine fibroids as monotherapy
- Phase 3 development in uterine fibroids and endometriosis
  - 40 mg relugolix once daily with E2/NETA*

LINZAGOLIX[3]

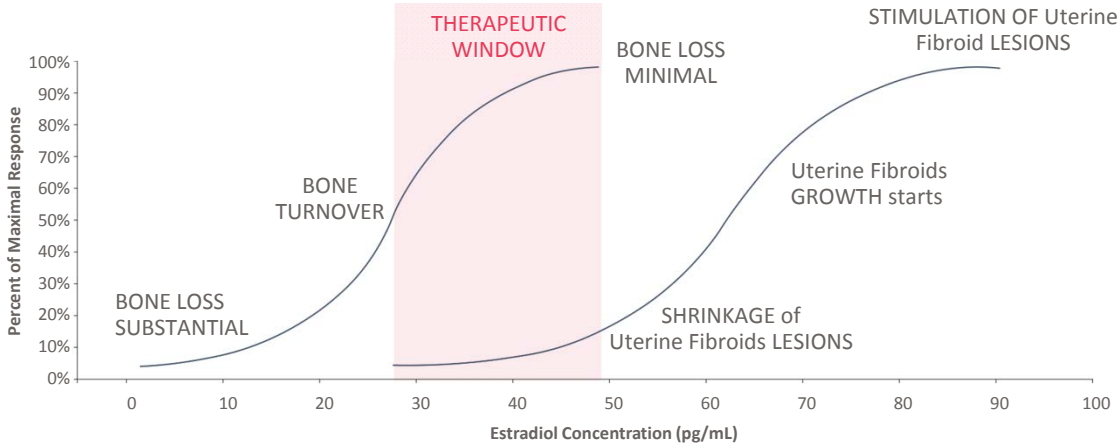


- Phase 3 development in uterine fibroids
  - 100 mg once-daily monotherapy
  - 200 mg once daily with E2/NETA*

*estradiol 1 mg / norethindrone acetate 0.5 mg

1. Farris M et al. Therapeutics and Clinical Risk Management 2019:15:157-178
2. Elsharoud A et al. Drugs of the Future 2019, 44(2):131-143
3. http://www.jefferies.com/CMSFiles/Jefferies.com/files/ObsEva.pdf

Estradiol Levels Within the Therapeutic Window May Improve Symptoms and Maintain Bone Health



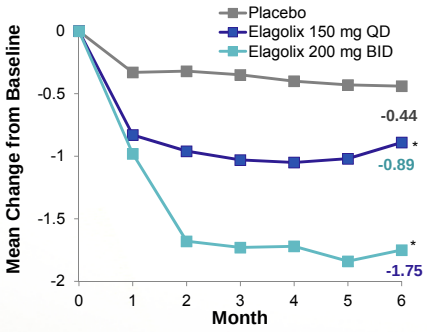
Adapted from Barbieri RL et al.[1]

1. Barbieri RL. Am J Obstet Gynecol1992; 166(2): 740-745.

Effect of Elagolix on Dysmenorrhea Over Time

Change in Dysmenorrhea Score at Month 6

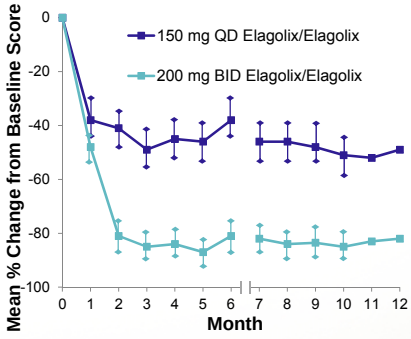
Baseline score approx. 2.1



Elaris EM-I

Effect of Elagolix on Dysmenorrhea Over 12 Months of Continuous Treatment

Baseline score approx. 2.1



Elaris EM-I | Elaris EM-III

*P<0.001; Bars represent 95% CI; N range across studies/doses: Baseline=138-149; Extension Month 1=136-148; Extension Month 6=110-122.
BID: *bis in die*; QD: *quaque die*.
1. Taylor H et al. N Engl J Med 2017; 377:28-40; 2. Surrey E et al. Obstet Gynecol 2018; 132:147-160.
3. ORILISSA (elagolix) Product Monograph. AbbVie Corporation October 2018.

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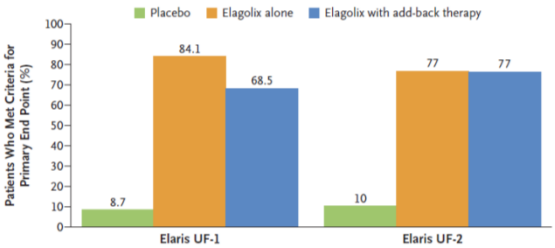
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

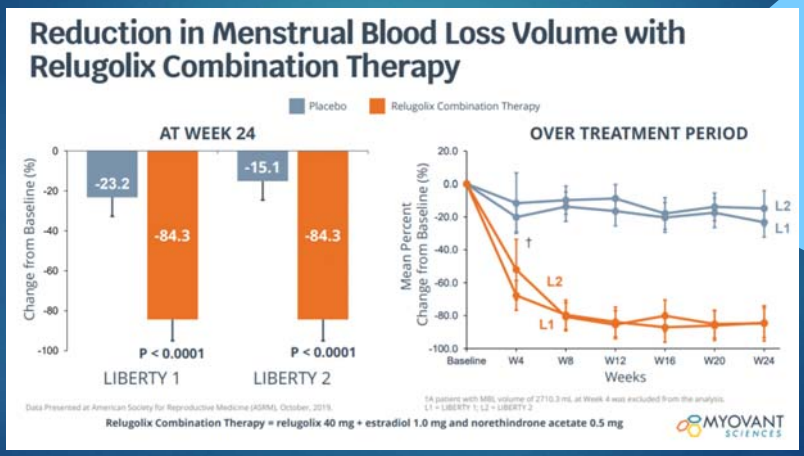
Elagolix for Heavy Menstrual Bleeding in Women with Uterine Fibroids

ELAGOLIX FOR HEAVY MENSTRUAL BLEEDING AND FIBROIDS



Difference from placebo — % (95% CI)		75.4 (66.2–84.6)	59.8 (51.1–68.5)		66.4 (55.5–77.3)	66.0 (57.1–75.0)
Risk ratio (95% CI)		9.7 (5.0–18.9)	7.9 (4.1–15.5)		7.1 (3.8–13.4)	7.2 (3.9–13.5)
Two-sided P value			<0.001			<0.001
No. of women	102	104	206	94	95	189
No. imputed by multiple imputation	8	3	16	6	11	12

Relugolix



The Hallmark of Menopause

Vasomotor Symptoms (VMS):

- Hot flushes and night sweats affect 75% of peri/postmenopausal women
- VMS have been associated with:
  - Poorer health condition or poorer health status
  - Reduced work productivity
  - Impaired quality of life

NAMS. Menopause Practice: A Clinician's Guide, 5th Ed., 2014.

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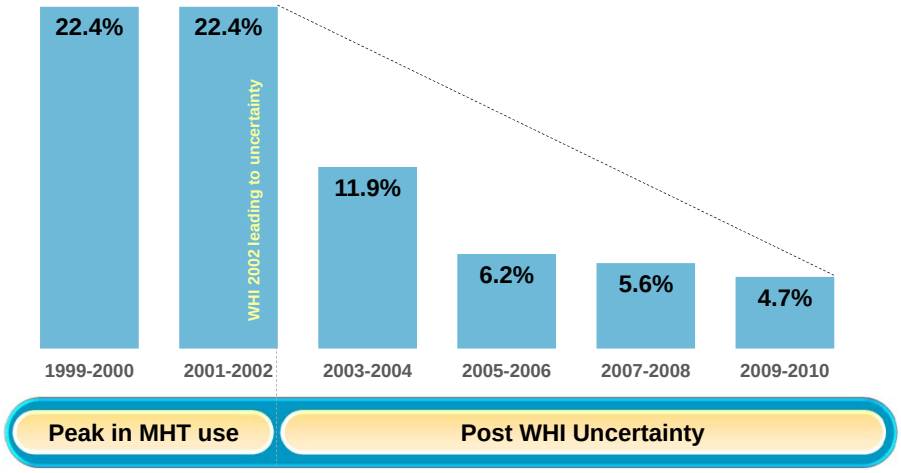
Decline in Use of Hormone Therapy Over Time



Sprague et al. *Obstet Gynecol* 2012;120(3):595–603.

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2017 NAMS Hormone Therapy Position Statement

- HT is the most effective treatment for VMS and GSM and has been shown to prevent bone loss and fracture
- Benefits are mostly likely to outweigh risks for symptomatic women who initiate HT when aged <60 years or who are within 10 years of menopause onset

NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

GSM, genitourinary syndrome of menopause; HT, hormone therapy; VMS, vasomotor symptoms

NAMS Position Statement. *Menopause* 2017;24(7):728-53.

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Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence

Collaborative Group on Hormonal Factors in Breast Cancer*

Summary

Background Published findings on breast cancer risk associated with different types of menopausal hormone therapy (MHT) are inconsistent, with limited information on long-term effects. We bring together the epidemiological evidence, published and unpublished, on these associations, and review the relevant randomised evidence.

Methods Principal analyses used individual participant data from all eligible prospective studies that had sought information on the type and timing of MHT use; the main analyses are of individuals with complete information on this. Studies were identified by searching many formal and informal sources regularly from Jan 1, 1992, to Jan 1, 2018. Current users were included up to 5 years (mean 1·4 years) after last-reported MHT use. Logistic regression yielded adjusted risk ratios (RRs) comparing particular groups of MHT users versus never users.

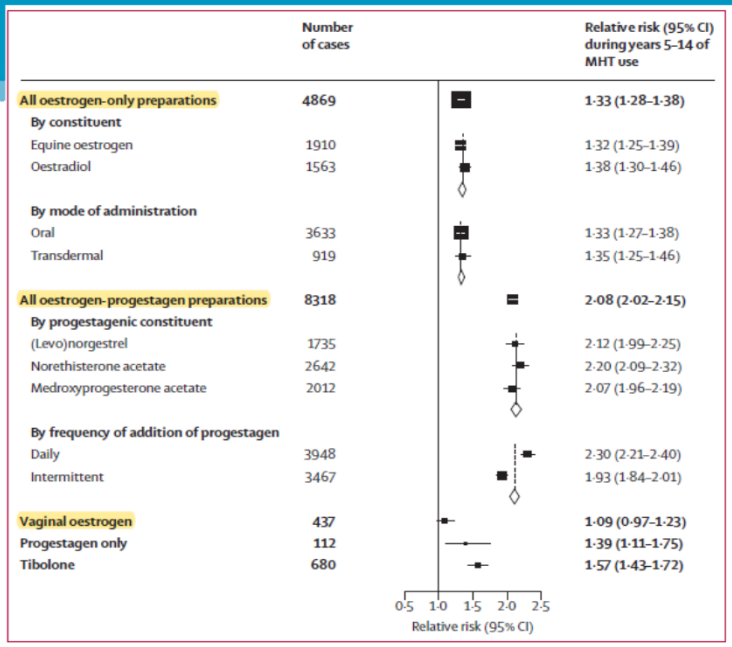
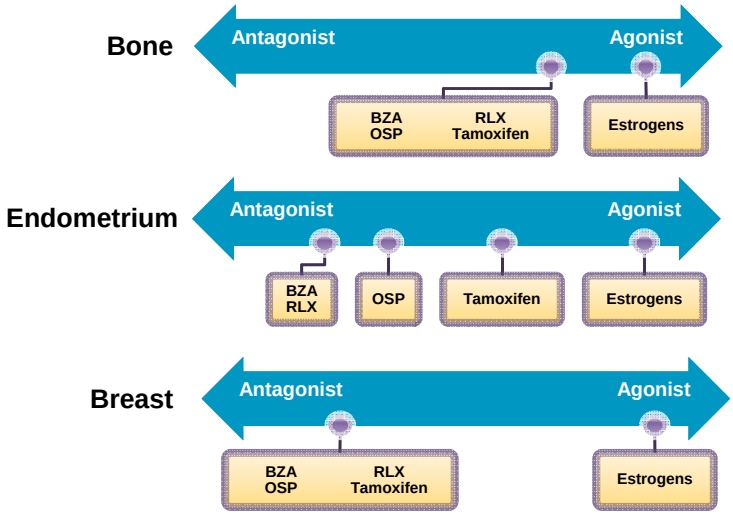


Figure 4: Main types of MHT: relative risks during years 5–14 of current use

Site of Action of SERMs



BZA, bazedoxifene; OSP, ospemifene; RLX, raloxifene; SERM, selective estrogen receptor modulator.
Adapted from Hadji. *Climacteric* 2012;15:513-23; and Maximov et al. *Curr Clin Pharmacol* 2013;8:135-55.

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Tissue-Selective Estrogen Complexes (TSECs)

TSEC

The purposeful pairing of a SERM with one or more estrogens to achieve pharmacologic results based on their blended tissue-selective activity profile[1,2]

1. Komm. *Reprod Sci* 2008;15(10):984–92; 2. Berrodin et al. *Mol Endocrinol* 2009;23(1):74–85.

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CE/BZA (DUAVIVE) Dosage & Administration

- One DUAVIVE tablet taken orally around the same time every day
- Tablet should be swallowed whole with fluid and not divided, crushed, chewed or dissolved in mouth
- Taken at any time of day, with or without food
- After opening foil pouch, product must be used within 45 days
- Duration of use should be consistent with treatment goals and benefits and risks for the individual

CE		SERM
Conjugated Estrogens 0.45 mg	+	Bazedoxifene 20 mg (Selective Estrogen Receptor Modulator)

DUAVIVE™ Product Monograph

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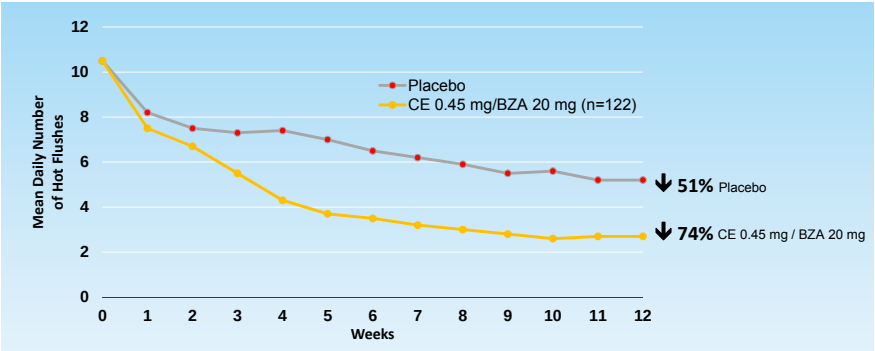
CE/BZA Results

Reduction in Mean Daily Number of Moderate to Severe Hot Flushes

Significant decreases in the number of hot flushes vs. placebo from week 3 to 12 for CE/BZA (P=0.008); MITT population (LOCF).



At week 12, CE 0.45 mg/BZA 20 mg significantly reduced hot flushes from baseline by 74% (10.3 to 2.8) compared to 51% (10.5 to 5.4) for placebo.

BZA, bazedoxifene, CE, conjugated estrogens; LOCF, last observation carried forward; MITT, modified intent-to-treat.

Pinkerton et al. *Menopause* 2009;16(6):1116-24.

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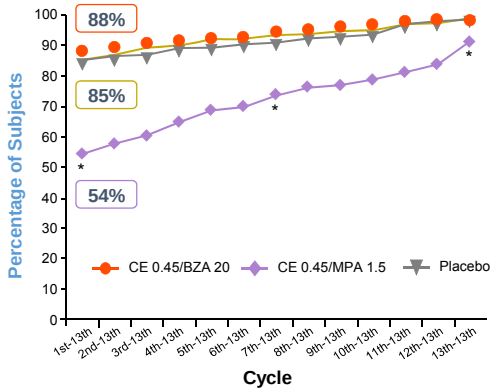
Rates of Bleeding/Spotting and Amenorrhea Similar to Placebo

Percentage of subjects with cumulative amenorrhea during consecutive 4-week periods (cycles) in SMART-5



- High and similar cumulative rates of amenorrhea at year 1 among women treated with CE/BZA and placebo; and was higher than seen in women treated with CE 0.45/ MPA 1.5
- Noncumulative rates of spotting and bleeding/spotting were similar among women treated with CE/BZA or placebo and consistently higher in women treated with CE 0.45/MPA 1.5

BZA, bazedoxifene; CE, conjugated estrogens; MPA, medroxyprogesterone acetate. *P<0.001 vs all other treatment groups.

Pinkerton et al. *J Clin Endocrinol Metab* 2014;99(2):189-98.

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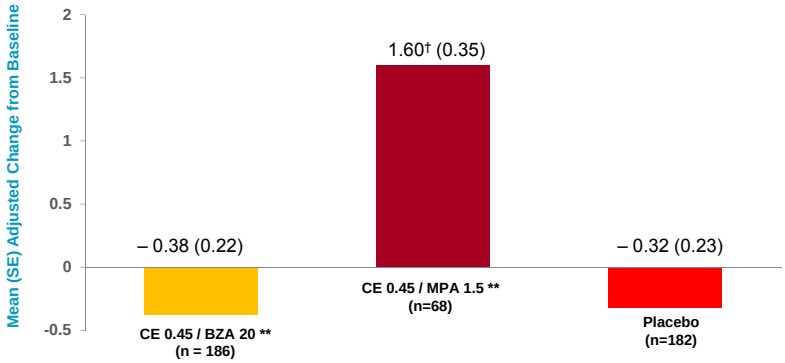
Change in Breast Density at 1 Year*

Neutral effect of CE/BZA, but not CE/MPA, on adjusted change from baseline in % breast density vs. placebo (P<0.001) at year 1



*Modified intent-to-treat population included all participants enrolled in the breast density substudy who took ≥1 doses of the study drug, had a baseline breast density evaluation and had ≥1 postbaseline evaluations. †P<0.001 vs. placebo. ** All doses mg/day
Note that CE/BZA and placebo arms not significantly changed from baseline despite negative values.
BZA, bazedoxifene; CE, conjugated estrogens; MPA, medroxyprogesterone acetate; SE, standard error.

Pinkerton et al. *Obstet Gynecol* 2013;121(5):959-68; Pinkerton et al. *Menopause* 2009;16(6):1116-24.

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What Is ᶜTibella® (tibolone)?

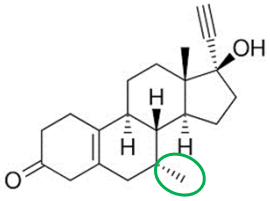
- Tibolone is a well-established treatment for climacteric complaints and prevention of osteoporosis in post-menopausal women in Europe
- Used in Europe since 1988
- Available in 90+ countries

ᶜTibella® is approved in Canada for short-term treatment of vasomotor symptoms due to estrogen deficiency in postmenopausal women, more than one year after menopause

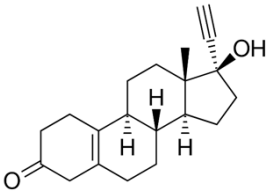
BioSyent

ᶜTibella

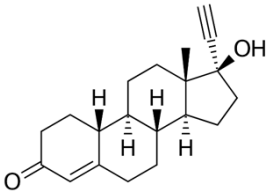
Molecular Structure



Tibolone



Norethynodrel



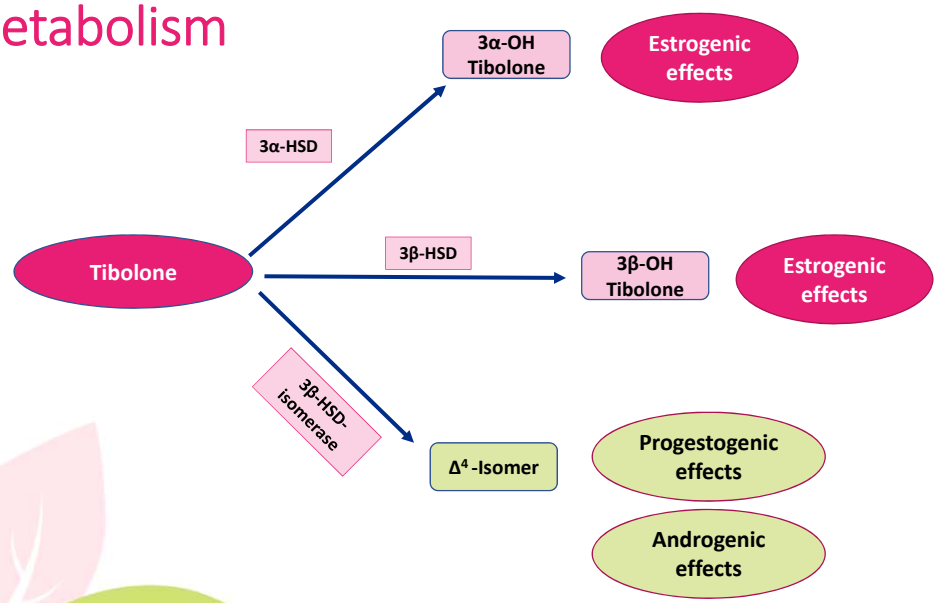
Norethisterone

The presence of the 7-methyl group means that the Δ^4-isomer is not subject to 5-reduction and therefore it retains its progestogenic activity in the endometrium for considerably longer period

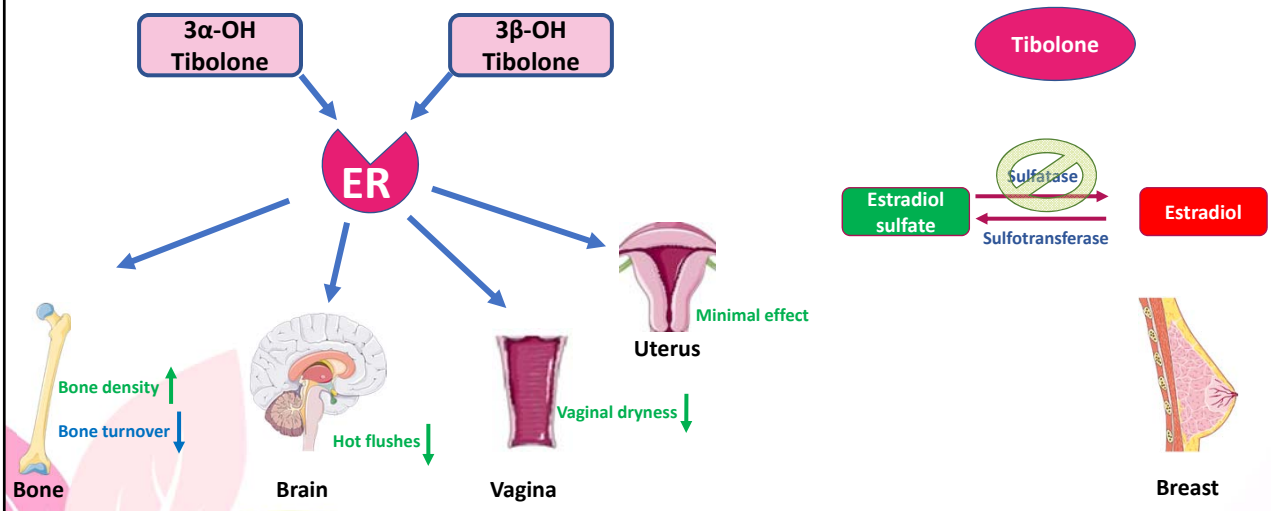
BioSyent

ᶜTibella

Metabolism

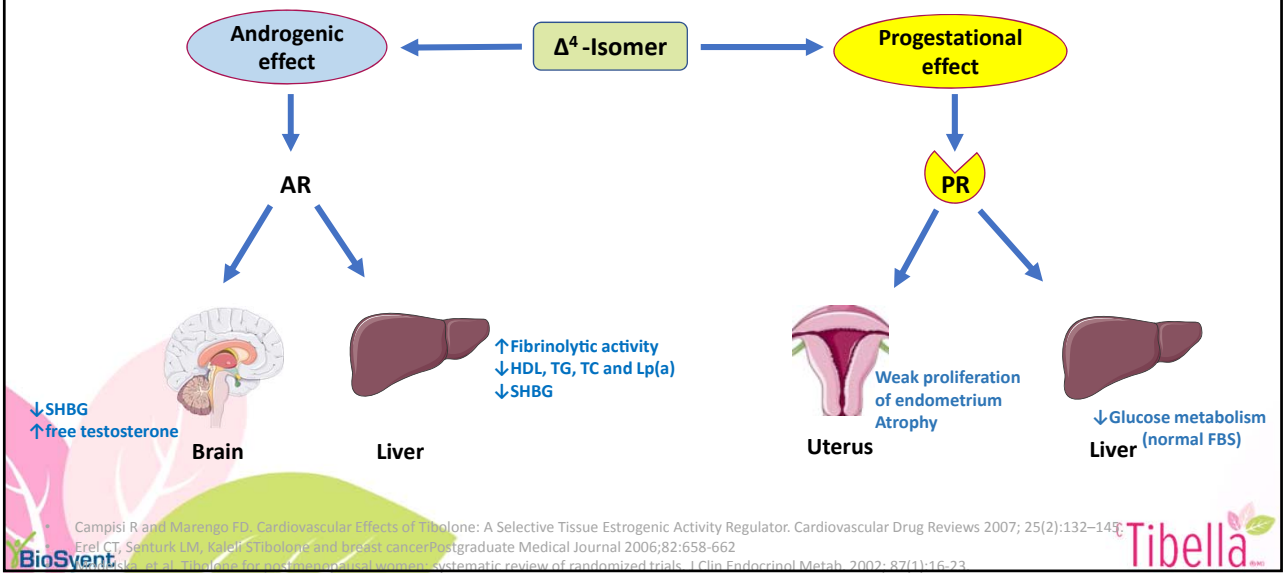


Pharmacodynamics: Estrogenic Effect



- Campisi R and Marengo FD. Cardiovascular Effects of Tibolone: A Selective Tissue Estrogenic Activity Regulator. Cardiovascular Drug Reviews 2007; 25(2):132–145.
- Erel CT, Senturk LM, Kaleli STibolone and breast cancerPostgraduate Medical Journal 2006;82:658-662
- Modelska et al. Tibolone for postmenopausal women: systematic review of randomized trials. J Clin Endocrinol Metab. 2002; 87(1):16-23.

Pharmacodynamics: Tibolone-Progestogenic and Androgenic Effects



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