Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update: Estrogens

Date of Review: August 2022

Date of Last Review: January 2017
Dates of Literature Search: 09/01/2016 - 04/04/2022

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- This review looks at whether new evidence should change the current policy for estrogens.
- Estrogens are taken by mouth, applied to the skin or inserted within the vagina.
- Estrogens and progestins are medicines used to treat hot flashes and other issues in people who are going through menopause. Providers also prescribe estrogens to people to prevent broken bones associated with bone disease and for some types of cancers.
- Use of estrogens increases risk of breast cancer, stroke, blood clots, gallbladder disease and urinary leakage. Estrogen applied to the skin have a lower risk of breast cancer than estrogens taken by mouth, but there is still an increased risk compared to taking no estrogen. People that have a uterus often take estrogen with a progestin to reduce the risk of endometrial cancer.
- Estrogens have both benefits and risks when used to prevent diabetes, colorectal cancers and heart disease. The United States Preventative Services Task Force (USPSTF) does not recommend estrogens for prevention of these conditions.
- Two new medicines are approved to treat menopause symptoms called Bijuva and Imvexxy. No studies show that they improve menopause symptoms compared to other estrogens.
- Fee-for-service (FFS) Medicaid pays for estrogen medicines. Certain estrogen medicines require the provider to explain why the specific estrogen in needed before paying for it. This is called a prior authorization.
- The Drug Use Research Management program and Pharmacy and Therapeutics Committee do not recommend any changes to the estrogen policy.

Purpose for Class Update:
A comprehensive literature search and evaluation on the comparative efficacy and safety of estrogen preparations was performed based on evidence published since the last update in 2017.

Research Questions:

1. Is there new comparative evidence on the effectiveness of estrogen therapies, used as monotherapy or in combination with progestins, for the treatment of menopausal symptoms or prevention of osteoporosis?
2. Is there new comparative evidence on the harms of estrogen products?
3. Are there subpopulations of women in which certain estrogen products have demonstrated superior efficacy or increased risk of harms?

Author: Kathy Sentena, PharmD

Conclusions:

- There were two systematic reviews, two guidelines, two safety warnings and two safety alerts identified since the last review in January of 2017.
- There is moderate quality evidence from a Cochrane review evaluating long-term hormone therapy (HT) (at least 1 year) for perimenopausal and menopausal women that HT reduces in the risk of fracture.[1] There is moderate quality evidence that combination HT increases the risk of stroke, venous thromboembolism (VTE) and gallbladder disease.[1]
- Hormone therapy for the primary prevention of chronic conditions in postmenopausal women was the focus of a 2017 Agency for Healthcare Research and Quality (AHRQ) review.[2] There is moderate to high quality evidence demonstrating the risk of diabetes and fractures is reduced with the use of estrogen alone. Combination estrogen and progestin therapy was found to decrease the risk of colorectal cancers, diabetes and fractures based on moderate to high quality of evidence. Increased risk of harms associated with estrogen use and combination HT included: gallbladder disease, breast cancer, stroke, VTE and urinary incontinence.[2]
- Guideline updates from National Institute for Health and Care Excellence (NICE) and the European Alliance of Associations for Rheumatology (EULAR) support the current policy on estrogens.[3,4]
- Two new formulations of estradiol were approved since the last review. Estradiol/progesterone 1 mg/100 mg combination product (Bijuva) capsules were approved for the use of moderate to severe vasomotor symptoms based on one placebo-controlled trial.[5] Estradiol vaginal inserts (Imvexxy) 4 mcg and 10 mcg were approved for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.[6]
- There was insufficient evidence on subgroup populations, such as differences in ethnicities and race, time since onset of menopausal symptoms and women with an intact uterus.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on evaluation of the clinical evidence.
- After evaluation of costs in executive session, make the following estrogens preferred: PREMPRO, PREMARIN, PREMPHASE, ANGELIQ, ELESTRIN, FEMRING, ESTRING, estradiol cream, and ESTRACE.

Summary of Prior Reviews and Current Policy:

- No changes were made to the estrogen derivatives PDL as a result of the update in 2017.
- Current policy consists of a prior authorization (PA) criteria requiring an Oregon Health Plan (OHP) approved diagnosis.

Background:

Estrogens are part of hormone replacement therapy used for reducing menopausal symptoms.[1] Estrogen is often used in combination with progestin products. The FDA approved uses for HT are for the treatment of menopausal symptoms and prevention of osteoporosis.[2] Estrogen is also used off-label for gender dysphoria disorder and palliative care in metastatic breast and prostate cancer.[7]

Menopause causes decreased estrogen levels with corresponding cessation of menstrual cycle, vasomotor symptoms, musculoskeletal, urogenital and psychological symptoms.[3] Symptoms can be associated with decreased quality of life affecting families and work environments. Menopause alone has been identified as a risk factor for cardiovascular disease (CVD).[2] Approximately 60% to 80% of women experience menopausal symptoms, 20% of them are considered severe symptoms. Prevalence varies between different ethnic groups and cultures, with a higher incidence in Black and Hispanic women.[8]

Treatment recommendations for menopausal symptoms include the use of lubricants and gels as well as lifestyle modifications (e.g., weight loss, smoking cessation). Estrogen products are considered the most effective treatment for vasomotor symptoms and should be considered in women who need additional treatment for menopausal symptoms who do not have contraindications. In women with an intact uterus, estrogen is given in combination with progestins to avoid hyperplasia or carcinoma.[8] A reduction in 50% or more in the frequency and severity of vasomotor symptoms is considered a clinically meaningful effect.[8] Estrogen is available as the following dosage formulations: oral, vaginal, intranasal, transdermal or subcutaneous implant. Estrogen derivatives include estradiol, estradiol valerate synthetic conjugated estrogens, ethinyl estradiol, or conjugated equine estrogen (**Appendix 1**).

Evidence for the long-term benefits and risks of HT has been mixed. Findings from the Women's Health Initiative (WHI) found HT prevented fractures and colon cancer, but noted an increased risk of cardiovascular (CV) events and breast cancer.[9] Mixed evidence has also suggested the use of HT in older women for prevention of CV disease, osteoporosis and cognitive decline. Observational studies of HT have demonstrated a reduced risk of coronary heart disease (CHD); however, findings from randomized controlled trials (RCTs) failed to demonstrate CHD benefits.[2] The United States Preventative Services Task Force (USPSTF) recommends against the use of HT for the primary prevention of chronic conditions.[10]

Oregon Health Plan (OHP) fee-for-service (FFS) population 125 women received oral estrogen products (99% preferred formulations), 35 patients received topical estrogen products (100% preferred formulations) and 22 patients received transdermal estrogen products (49% preferred formulations) based on claims from the first quarter of 2022. The overall cost for the class does not represent a substantial monetary burden to OHP.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines.

New Systematic Reviews:

Hormone Replacement Therapy

Cochrane – Long-term Hormone Replacement Therapy for Perimenopausal and Postmenopausal Women
A 2017 review evaluated the literature to determine the effects of long-term HT, at least 1 year's timeframe, on mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition in perimenopausal and postmenopausal women.[1] The use of HT (e.g., estrogens with or without progestins) were included in the systematic review. Routes of administration included oral, transdermal, subcutaneous, or intranasal. Most studies used moderate doses of estrogen (e.g., conjugated equine estrogens [CEE] 0.625 mg daily, estradiol 1 mg, transdermal estradiol 0.05 mg twice weekly). The dose of progesterone used in continuous combination estrogen and progesterone regimens were the following; medroxyprogesterone acetate (MPA) 2.5 mg daily, MPA 10 mg daily and 1 mg norethindrone daily. Twenty-two studies were included (n=43,637) involving predominately healthy postmenopausal women of whom most were 60 years and

older (range of 26 to 91 years).[1] Only 30% of women were 50-59 years, which is the age of women who most often seek the use of estrogen for the management of vasomotor symptoms.[1] Most of the evidence was found to be at low risk of bias.

The use of combined continuous HT, moderate dose estrogen and medroxyprogesterone, was associated with moderate quality of evidence for all of the outcomes studied. Findings are presented in **Table 1**.[1] There were more coronary events, stroke, VTE, breast cancer, gallbladder disease and death from lung cancer with the use of HT compared to placebo. There was a reduction in the risk of clinical fractures with HT versus placebo. The use of estrogen only HT are also presented in **Table 1**. Moderate strength of evidence found an increased the risk of stroke, VTE with follow-up of 1-2 years and gallbladder disease with estrogen compared to placebo.[1] The risk of breast cancer and clinical fractures was reduced with the use of HT compared to placebo. There was no effect on the risk of coronary disease with the use of estrogen only HT.

Table 1. Hormone Therapy in Postmenopausal Women[1]

Outcome	Follow-up	Results	Quality of Evidence
Combined Continuous Hormone Therapy Compared to Placebo			
Coronary events (MI or cardiac death)	Mean/median 1 year	RR 1.89 (95% CI, 1.15 to 3.10)	Moderate
Stroke	Mean 3 years	RR 1.46 (95% CI, 1.02 to 2.09)	Moderate
Venous thromboembolism (DVT or PE)	Mean/median 1 year	RR 4.28 (95% CI, 2.49 to 7.34)	Moderate
Breast cancer	Median 5.6 years	RR 1.27 (95% CI, 1.03 to 1.56)	Moderate
Death from lung cancer	Median 8 years	RR 1.74 (95% CI, 1.18 to 2.55)	Moderate
Gallbladder disease	Mean 5.6 years	RR 1.64 (95% CI, 1.30 to 2.06)	Moderate
All clinical fractures	Mean 5.6 years	RR 0.78 (95% CI, 0.71 to 0.86)	Moderate
Estrogen Only Hormone Therapy compared to Placebo			
Coronary events (MI or cardiac death)	Mean 7.1 years	RR 0.94 (95% CI, 0.78 to 1.13)	Moderate
Stroke	Mean 7.1 years	RR 1.33 (95% CI, 1.06 to 1.67)	Moderate
Venous thromboembolism (DVT or PE)	1-2 years	RR 2.22 (95% CI, 1.12 to 4.39)	Moderate
Venous thromboembolism (DVT or PE)	Mean 7.1 years	RR 1.32 (95% CI, 1.00 to 1.74)	Moderate
Breast cancer	Mean 7.1 years	RR 0.79 (95% CI, 0.61 to 1.01)	Moderate
Gallbladder disease	Mean 7.1 years	RR 1.78 (95% CI, 1.42 to 2.24)	Moderate
All clinical fractures	Mean 7.1 years	RR 0.73 (95% CI, 0.65 to 0.80)	Moderate

Abbreviations: CI – confidence interval; DVT – deep vein thrombosis; MI – myocardial infarction; PE – pulmonary embolism; RR – relative risk.

There is good evidence for the use of HT for relief of menopausal symptoms associated with menopause. Evidence suggests additional benefit for prevention of postmenopausal osteoporosis but is reserved for patients who are unable to take non-estrogen options. Estrogens should not be used for primary or secondary prevention CV disease. Estrogens should be avoided in women who are at high risk of CV disease, thromboembolic disease or certain cancers (e.g., breast, uterine).[1]

AHRQ – Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women

The AHRQ did a systematic review and meta-analysis for the U.S. Preventive Services Task Force in 2017. The objective was to evaluate the benefits and risks of HT for primary prevention of chronic conditions in postmenopausal women.[2] Evidence was searched through August of 2016 and ongoing surveillance of the literature occurred through August 2017. Most studies included healthy women who were perimenopausal or postmenopausal with one year or more of HT. Seventeen fair-quality trials were identified and met eligibility criteria for inclusion into the review.[2] The WHI was the largest contributor to the data. Analyses were divided into those women who used estrogen alone and those who took combination therapy with estrogen and progestin therapy.

There are benefits and risks identified with both estrogen alone and combination estrogen plus progestin therapy (**Tables 2 and 3**).[2] There was no increased risk or benefit of all-cause mortality in women who took estrogen alone or estrogen plus progestin based on moderate to high quality of evidence.

Table 2. Risks and Benefits of Estrogen Monotherapy compared to Placebo[2]

Outcome	Population	Cases/Quality of Evidence
Benefits of Therapy		
Diabetes (new diagnosis requiring medication)	Per 10,0000 women over 6.8 to 7.2 years	137 fewer cases/moderate
Fractures	Per 10,000 women over 6.8 to 7.2 years	382 fewer cases/high
Risks of Therapy		
Gallbladder disease*	Per 10,000 women 5.4 to 7.1 years	213 more cases/moderate
Stroke	Per 10,000 women 5.4 to 7.1 years	79 more cases/moderate
Venous thromboembolism	Per 10,000 women 5.4 to 7.1 years	78 more cases/moderate
Urinary incontinence†	Per 10,000 women during a 1 year follow-up	1,261 more cases/moderate
Key: * Gallbladder disease was defined as cholecystitis and cholelithiasis); † Urinary incontinence was defined as stress, urge and overall		

Table 3. Risks and Benefits of Estrogen Plus Progestin Therapy compared to Placebo[2]

Outcome	Population	Cases/Quality of Evidence
Benefits of Therapy		
Colorectal cancer	Per 10,0000 women over 5.0 to 5.6 years	33 fewer cases/moderate
Diabetes (new diagnosis requiring medication)	Per 10,000 women over 5.0 to 5.6 years	77 fewer cases/moderate
Fractures	Per 10,000 women over 5.0 to 5.6 years	222 fewer cases/high
Risks of Therapy		
Invasive breast cancer	Per 10,000 women 4.0 to 5.6 years	52 more cases/high
Probable dementia	Per 10,000 women 4.0 to 5.6 years	88 more cases/moderate
Gallbladder disease	Per 10,000 women 4.0 to 5.6 years	116 more cases/moderate
Stroke	Per 10,000 women 4.0 to 5.6 years	53 more cases/high
Venous thromboembolism	Per 10,000 women 4.0 to 5.6 years	120 more cases/moderate
Urinary incontinence†	Per 10,000 women follow-up of 1 year	876 more cases/moderate
Key: * Gallbladder disease was defined as cholecystitis and cholelithiasis); † Urinary incontinence was defined as stress, urge and overall		

Limitations to the evidence were lack of comparisons between the different types, doses and delivery routes of HT. Subgroup analyses and trials were not powered to detect differences in preventative outcomes. There was insufficient data on the use of HT in women who were younger and nonwhite ethnicity.

After review, 16 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[11–26]

New Guidelines:
High Quality Guidelines:

NICE – Menopause: Diagnosis and Management
The National Institute for Health and Care Excellence originally published guidance for the management of menopause in 2015 and has since provided updates in 2019 and 2021.[3] All recommendations include routine assessment of symptoms to tailor therapy to current needs of women experiencing menopause. Treatment recommendations for management of menopausal symptoms are outlined in **Table 4**.[3] Vasomotor symptoms should not be treated with SSRIs, SNRIs, or clonidine as first-line treatment. Isoflavones or black cohosh may relieve vasomotor symptoms; however, preparation may vary, drug interactions have been reported, multiple preparations are available and safety is unknown.

Vaginal estrogens relieved symptoms of urogenital atrophy without the safety risks associated with systemic estrogen products. Oral HT increases the risk of VTE and can present early in treatment and increases with age.[3] The risk of VTE is not significantly increased with the use of transdermal products. After discontinuation of HT the increased risk of VTE is eliminated. Women who are at increased risk of VTE or who have a body mass index greater than 30 kg/m^2 should consider transdermal HT instead of oral therapy.[3] Additional risks with HT include an increased incidence of stroke; however, the evidence is low to very low quality. There was no additional CV risk noted with HT use in women under the age of 60 years and there was no increased risk of CV mortality. Low quality evidence found no increased risk of diabetes with the use of HT. The use of HT had no benefit or risk of developing or preventing dementia based on very low to moderate quality of evidence.[3] There is low to moderate quality of evidence that HT reduces the risk of fragility fracture, even upon HT discontinuation.

Additional safety updates on the increased risk of breast cancer with HT was added to the guidance.[27] The increased risk is with all HT preparations except for vaginal estrogens. The increased risk persists for more than 10 years after the HT is discontinued. The shortest duration and lowest dose of HT should be utilized.

Table 4. NICE Recommendations for Management of Menopausal Symptoms[3]

Symptom	Recommendation	Quality of Evidence
Vasomotor Symptoms	• Offer HT after discussing the short-term (up to 5 years) and longer-term benefits and risks • Options include: - Estrogen and progestin to women with a uterus - Estrogen alone to women without a uterus	• Very low to moderate quality • Limited data beyond 1 year
Urogenital Atrophy	• Vaginal estrogens should be offered (even if taking systemic HT) and continue treatment as long as needed to relieve symptoms • Vagina estrogens should be offered to women in whom HT is contraindicated	• Very low to moderate quality

Psychological Symptoms	• Recommended HT for women with low mood due to menopause • There is no clear evidence for the use of SSRIs or SNRIs to ease low mood in women with menopausal symptoms who have not been diagnosed with depression	• Very low quality of evidence
Altered Sexual Function	• Consider testosterone supplementation for menopausal women with low sexual desire if HT is not effective	• Very low quality of evidence
Abbreviations: HT – hormone therapy; SNRIs- serotonin norepinephrine reuptake inhibitors; SSRIs – selective serotonin reuptake inhibitors		

EULAR – Recommendations for Women's Health and the Management of Family Planning, Assisted Reproduction, Pregnancy and Menopause in Patients with Systemic Lupus Erythematosus and/or Antiphospholipid Syndrome

A 2017 guideline completed by EULAR updated the recommendations for the use of HT in women with systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS).[4] Guideline methodology was well described and authors reported no conflicts of interest. The evidence was graded from level 1 to 3, with level 1 evidence being the highest level, consisting of RCTs or meta-analyses, level 2 is sufficient evidence with questionable confidence in the evidence and level 3 being the lowest level of evidence. Grading of the recommendations ranged from A to D. Grade A is based on high level of evidence, Grade B recommendations are based on level 1 evidence with concerns of validity, Grade C is based on level 1 or 2 evidence and Grade D is based on expert opinion.[4] The focus of this review will be on the recommendations for the use of estrogens in women with SLE and/or APS. Other therapies will be discussed according to their corresponding class update. The use of estrogen products, as part of HT, can be used for women with severe vasomotor menopausal symptoms that have SLE which is stable/inactive based on negative antiphospholipid antibodies (aPL).[4] There is no evidence of severe exacerbations of SLE with the use of HT in RCTs lasting up to 24 months. In women with APS, the benefits of the use of HT should be weighed against the risk of thrombotic and CV risks. Evidence is limited on the optimal duration of HT; however, it is recommended that the shortest duration possible be used.

Additional Guidelines for Clinical Context:

Endocrine Society – Pharmacological Management of Osteoporosis in Postmenopausal Women

The recommendations for the use of HT were included in the guidelines for the management of osteoporosis in postmenopausal women issued by the Endocrine Society.[28] Recommendations were based off a systematic review and meta-analysis; however, specifics of the search were not included. The evidence was graded from very low quality to high quality. The strength of recommendations were designated as "recommended" and "we suggest" based on the evidence. Fifty percent of authors had conflicts of interest and funding was provided by the Endocrine Society, which partners with industry. Recommendations will be included for clinical context but not used for policy decisions.

The use of estrogen only HT is recommended for postmenopausal women with hysterectomy who are at high risk of fracture to prevent all types of fractures with the following patient characteristics; under 60 years of age or < 10 years past menopause; at low risk of deep vein thrombosis, those who are not candidates for the use of bisphosphonates or denosumab, bothersome vasomotor symptoms, climacteric symptoms, without contraindications, no history of stroke or myocardial infarction, without breast cancer, and willing to take HT.[28] This is a suggested recommendation supported by moderate quality of evidence.

After review, 5 guidelines were excluded due to poor quality or insufficient evidence.[29–33]

New Formulations or Indications:

Estradiol and progesterone capsules (Bijuva): In 2018 a new drug approval was granted for the estradiol/progesterone 1 mg/100 mg combination product indicated for women with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.[5] Combination estradiol/progesterone was shown to reduce moderate to severe vasomotor symptoms, frequency and severity, more than placebo in one 12-week, randomized, single-arm study (n=726). At 12 weeks reduction in mean weekly frequency of symptoms were reported as clinically meaningful with a difference from placebo in the estradiol/progesterone arm of -16.58; p<0.001.[5] The severity of weekly moderate to severe vasomotor symptoms was reduced with estradiol/progesterone by -0.57 (p<0.001) compared to placebo at week 12. Four cases of breast cancer were diagnosed over the year-long safety study, 2 in patients treated with estradiol/progesterone 0.5 mg/100 mg and 2 in the estradiol/progesterone 1 mg/100 mg and none in the placebo group. As with other estrogen products there is a black box warning for the risk of increased risk of stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction.[5] There is also evidence of increased risk of invasive breast cancer and probable increased risk of dementia in postmenopausal women, 65 years and older.

Estradiol vaginal inserts (Imvexxy): Estradiol vaginal inserts 4 mcg and 10 mcg were approved in 2018 for the treatment of moderate to severe dyspareunia, symptom of vulvar and vaginal atrophy, due to menopause.[6] Evidence for approval was from one 12-week, double-blind, placebo-controlled, study of 574 women who were postmenopausal. For moderate to severe symptoms of dyspareunia associated with postmenopausal vulvar and vaginal atrophy at 12 weeks compared to baseline were associated with reductions; estradiol 4 mcg, estradiol 12 mcg and placebo, -1.52 (p = 0.0149 compared to placebo), -1.69 (p<0.0001 compared to placebo) and -1.28, respectively.[6] As with other estrogen products there is a black box warning for the risk of increased risk of stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction.[6] There is also evidence of increased risk of invasive breast cancer and probable increased risk of dementia in postmenopausal women, 65 years and older.

New FDA Safety Alerts:

Table 5. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Estradiol Topical[34]	Divigel Vivelle-DOT	December 2019 October 2021	Boxed Warning	The boxed warning was updated to document that the risk of increased adverse CV events and dementia seen with higher CE doses with lower have not been fully studied and these risks can't be excluded with lower CE doses. The risk of CV events, dementia and breast cancer with combination therapy (e.g., low CE with MPA), have also not been studied and therefore, an increased risk cannot be excluded. The risks and benefits should be discussed with the patient.
Estradiol Topical[34]	Climara Alora Estraderm Minivelle Elestrin Estrogel Divigel Menostar	November 2017	Warnings and Precautions	There is evidence for an increased risk of ovarian cancer with the use of HT. The exact duration of HT use associated with an increased risk of ovarian cancer is not known.

Abbreviations: CE – conjugated estrogens; CV – cardiovascular; COC - combination oral contraceptives; HT – hormone therapy; MPA – medroxyprogesterone acetate.

Randomized Controlled Trials:

No new RCTS were identified. A total of 1,168 citations were manually reviewed from the literature search. Only trials reporting new comparative evidence were considered for inclusion. After manual review RCTs were excluded due to wrong study design, comparator, outcome studied, or lack of reported comparative outcome data.

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Appendix 1: Current Preferred Drug List

Estrogens, Oral

Generic	Brand	Form	PDL
estradiol	ESTRACE	TABLET	Y
estradiol	ESTRADIOL	TABLET	Y
estrogens,conj.,synthetic A	CENESTIN	TABLET	Y
estropipate	ESTROPIPATE	TABLET	Y
estropipate	OGEN	TABLET	Y
drospirenone/estradiol	ANGELIQ	TABLET	N
estradiol/norethindrone acet	ACTIVELLA	TABLET	N
estradiol/norethindrone acet	AMABELZ	TABLET	N
estradiol/norethindrone acet	ESTRADIOL-NORETHINDRNE ACETAT	TABLET	N
estradiol/norethindrone acet	LOPREEZA	TABLET	N
estradiol/norethindrone acet	MIMVEY	TABLET	N
estradiol/norgestimate	PREFEST	TABLET	N
estradiol/progesterone	BIJUVA	CAPSULE	N
estrogen,con/m-progest acet	PREMPHASE	TABLET	N
estrogen,con/m-progest acet	PREMPRO	TABLET	N
estrogen,ester/me-testosterone	ESTRATEST	TABLET	N
estrogen,ester/me-testosterone	ESTRATEST H.S.	TABLET	N
estrogen,ester/me-testosterone	ESTROGEN-METHYLTESTOSTERONE	TABLET	N
estrogen,ester/me-testosterone	SYNTEST D.S.	TABLET	N
estrogens, conjugated	PREMARIN	TABLET	N
estrogens,conj/bazedoxifene	DUAVEE	TABLET	N
estrogens,esterified	ESTRATAB	TABLET	N
estrogens,esterified	MENEST	TABLET	N
norethindrone ac-eth estradiol	FEMHRT	TABLET	N
norethindrone ac-eth estradiol	FYAVOLV	TABLET	N
norethindrone ac-eth estradiol	JINTELI	TABLET	N
norethindrone ac-eth estradiol	NORETHINDRON-ETHINYL ESTRADIOL	TABLET	N

Estrogens, Topical

Generic	Brand	Form	PDL
estradiol	ALORA	PATCH TDSW	Y
estradiol	DOTTI	PATCH TDSW	Y
estradiol	ESTRADERM	PATCH TDSW	Y
estradiol	ESTRADIOL (TWICE WEEKLY)	PATCH TDSW	Y
estradiol	LYLLANA	PATCH TDSW	Y
estradiol	MINIVELLE	PATCH TDSW	Y
estradiol	VIVELLE-DOT	PATCH TDSW	Y

estradiol	CLIMARA	PATCH TDWK	Y
estradiol	ESTRADIOL (ONCE WEEKLY)	PATCH TDWK	Y
estradiol	ELESTRIN	GEL MD PMP	N
estradiol	ESTROGEL	GEL MD PMP	N
estradiol	DIVIGEL	GEL PACKET	N
estradiol	MENOSTAR	PATCH TDWK	N
estradiol	EVAMIST	SPRAY	N
estradiol/levonorgestrel	CLIMARA PRO	PATCH TDWK	N
estradiol/norethindrone acet	COMBIPATCH	PATCH TDSW	N

Estrogens, Vaginal

Generic	Brand	Form	PDL
estradiol	ESTRADIOL	TABLET	Y
estradiol	VAGIFEM	TABLET	Y
estradiol	YUVAFEM	TABLET	Y
estrogens, conjugated	PREMARIN	CREAM/APPL	Y
estradiol	ESTRACE	CREAM/APPL	N
estradiol	ESTRADIOL	CREAM/APPL	N
estradiol	ESTRING	VAG RING	N
estradiol acetate	FEMRING	VAG RING	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to April 04, 2022
Search Strategy:

#	Searches	Results
1	vasomotor system.mp. or Vasomotor System/	9471
2	Osteoporosis, Postmenopausal/	13826
3	hypoestrogenism.mp.	496
4	vagina atrophy.mp.	3
5	vulva atrophy.mp.	0
6	estrogen replacement therapy.mp. or Estrogen Replacement Therapy/	16825
7	estrogen.mp. or Estrogens/	186764
8	estradiol.mp. or Estradiol/	128143
9	estropipate.mp.	61
10	ethinyl estradiol.mp. or Ethinyl Estradiol/	10611
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	278558
12	limit 11 to (english language and humans and yr="2016 -Current")	26502
13	limit 12 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review")	1168

Appendix 3: Key Inclusion Criteria

Population	Women with menopausal symptoms, individuals with hypoestrogenism or osteoporosis
Intervention	Estrogen derivatives (monotherapy and with progestins)
Comparator	Placebo or other active treatments for menopausal symptoms, hypoestrogenism, or postmenopausal osteoporosis prevention
Outcomes	Improvement in the frequency or severity of menopausal symptoms, estrogen levels or decreased fracture rates
Timing	Onset of mild to moderate menopausal symptoms or relevant diagnosis
Setting	Outpatient

Estrogen Derivatives

Goal(s):

- Restrict use to medically appropriate conditions funded under the OHP

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred estrogen derivatives
- All estrogen derivatives for patients <18 years of age

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the estrogen requested for a patient ≥18 years old?	**Yes:** Go to #3	**No**: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months.
4. Is the medication requested for gender dysphoria (ICD10 F642, F641)?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Have **all** of the following criteria been met? • Patient has the capacity to make fully informed decisions and to give consent for treatment; and • If patient <18 years of age, the prescriber is a pediatric endocrinologist; and • The prescriber agrees criteria in Guideline Notes on the OHP List of Prioritized Services have been met. See: https://www.oregon.gov/oha/HPA/DSI-HERC/SearchablePLdocuments//Prioritized-List-GN-127.docx	**Yes:** Approve for up to 6 months	**No**: Pass to RPh. Deny; medical appropriateness
6. Is the medication requested for hypogonadism?	**Yes:** Approve for up to 6 months	**No**: Go to #7
7. RPh only: All other indications need to be evaluated to see if funded under the OHP.	If funded and prescriber provides supporting literature: Approve for up to 12 months.	If non-funded: Deny; not funded by the OHP

P&T / DUR Review: *8/22 (KS), 1/17 (SS); 11/15 (KS)*
Implementation: *4/1/17; 1/1/16*