



# Hormone Replacement Therapies for Perimenopause and Menopause: Provider Guide

*Information for providers on hormone replacement treatment options, dosing, and safety factors for perimenopause and menopause symptoms.*



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# Background and Safety

Menopause can cause a variety of symptoms in patients that can affect daily life, mental health, well-being, and maintaining readiness. For providers treating menopause symptoms, hormone replacement treatments are the gold standard.

## BACKGROUND

- **Menopausal symptoms include genitourinary symptoms** such as vaginal dryness, burning, and painful intercourse, or **systemic symptoms** such as vasomotor symptoms (hot flashes), mood swings, brain fog **and behavioral changes**.
- **Symptoms of menopause are related to dropping Estrogen levels.**
- These **symptoms can be severe and limit a healthy lifestyle**, daily function, sexual health, and overall well being.
- **The normal female menstrual cycle stops at approximately age 51-52** at which time the ovaries are secreting less and less estrogen responsible for the symptoms.
- **Menopause prior to the age of 40 would be considered premature ovarian insufficiency** warranting further investigation.
- **Menopausal symptoms can start 5-10 years prior to the cessation of menses** so treatment may be indicted for perimenopausal symptoms as well.
- **The best therapy for the symptoms of menopause is hormone replacement (HRT)** for estrogen and progesterone.
- In patients that are **unable to take hormone replacement there are alternatives**, however, these may not be as effective.

## SAFETY

- Recent research has found that the **absolute risk of HRT is low** and women within 10 years of menopause had **no significant increased risk of cardiovascular disease**, stroke, or embolism over baseline.
- **Prior to initiating HRT, you should assess a patient's cardiovascular risk status.** Patients with a history of heart attack, stroke, venous thromboembolism, hypertension, hyperlipidemia, are obese, or use tobacco have increased risk, and HRT is not advised.
- **Patients that have a uterus will need a progesterone to counteract the effects of estrogen** on the endometrial lining. Unopposed estrogen medication can lead to hyperplasia and cancer in some cases.



# Dosing and Approved Formulations

When treating menopause symptoms, hormone replacement treatments are the gold standard. There are approved formulations of hormone replacement that providers can counsel patients on.

## APPROVED FORMULATIONS

<b>Estrogen</b>	<p>Approved routes: oral tablets, transdermal preparations and patches, gels/emulsions/sprays, and vaginal rings.</p> <ul style="list-style-type: none"> <li><i>Use of topical or vaginal estrogen may pose less risk of cardiovascular side effects and may not interfere with other medications.</i></li> </ul>
<b>Progesterone</b>	<p>Approved routes: oral progesterone combination formulations, oral micronized progesterone, progesterone intrauterine device (IUD).</p> <ul style="list-style-type: none"> <li><i>Micronized progesterone is a bioidentical formulation that is now recommended as first line therapy given less cardiovascular side effects than synthetic progestin</i></li> <li><i>Patient opting to use cyclic progesterone therapy may/will experience menstrual like bleeding or spotting and should be counselled about this side effect. Continuous dosing may be more tolerable.</i></li> <li><i>Levonorgestrel IUD is a good alternative for patients unable to tolerate systemic progesterone. Though effective for 5 years, Mirena IUD is not FDA approved for this indication</i></li> </ul>
<b>Combination Therapy</b>	<p>Oral tablets, topical/patch applications.</p>

## DOSING

- The American College of Obstetrics and Gynecology (ACOG) [recommends](#) that HRT be used for the shortest duration at the lowest effective dose, recommending that women taper off HRT after 2-3 years.
- New [data](#) suggests that patients maintained on lower doses of HRT can effectively do so without additional risk beyond age 65. This may limit the return of bothersome menopausal symptoms that return upon cessation of HRT use.
- Systemic HRT should be given in the lowest dose and for the shortest period possible to decrease the risk of serious adverse events, such as thromboembolic disease and breast cancer.
- Specific recommendations on dosing can be found on the following page.



# Approved Formulations

The following chart includes a provider guide for approved HRT formulations to treat vasomotor symptoms (e.g., hot flashes). Please note that some treatments require prior authorizations or specialist approval.

## HRT Approved for Vasomotor Symptoms

\*Oral and transdermal routes are preferred over injection

Medication Name	Generic Name	Route	Dose
Climara®	Estradiol	Transdermal Patch	0.025mg-0.1mg released per day, patch applied weekly
ClimaraPro®	Estradiol /Levonorgestrel	Transdermal Patch	0.045mg/0.015mg released per day, patch applied weekly
Combi-patch®	Estradiol /Norethindrone	Transdermal Patch	0.05mg/0.14mg or 0.05mg/0.25mg released per day, patch applied twice weekly
Vivelle-Dot®	Estradiol	Transdermal Patch	0.025mg-0.1mg released per day, patch applied twice weekly
Duavee®	Conjugated Estrogen/ Bazedoxifene	Oral	0.45mg/20mg daily (SERM combination formulation, does not require use of progesterone)
Estrace®	Micronized estradiol-17B	Oral	0.5 to 1 mg daily
Premarin®	Conjugated estrogen (CEE)	Oral	0.3 to 0.625mg daily
PremPro®	CEE/Progestin	Oral	0.3/1.5mg-0.625/5mg daily
Bijuva®	Estradiol 17B/progesterone	Oral	0.5/100mg or 1/100mg daily
Angeliq®	CEE/drospirenone	Oral	0.5/0.25mg or 1/0.5mg daily
Depo-Estradiol®*	Estradiol Cypionate	Injection	5mg/ml every 4wks
Delestrogen®*	Estradiol Valerate	Injection	10-40mg/ml every 4wks



# Approved Formulations

The following charts include provider guides for approved HRT formulations for Progesterone co-use and to treat vaginal symptoms (e.g., vaginal dryness, burning, and painful intercourse). Please note that some treatments require prior authorizations or specialist approval.

## Progesterone Formulations for Co-Use with HRT

Medication Name	Route	Dose
Climara©	Transdermal Patch	0.025mg-0.1 mg released per day, patch applied weekly
ClimaraPro©	Transdermal Patch	0.045mg/0.015mg released per day, patch applied weekly
Combi-patch©	Transdermal Patch	0.05mg/0.14mg or 0.05mg/0.25mg released per day, patch applied twice weekly
Vivelle-Dot©	Transdermal Patch	0.025mg-0.1 mg released per day, patch applied twice weekly

## Formulations Approved for Vaginal Symptom Treatment

Medication Name	Generic Name	Route	Dose
Climara©	Estradiol	Transdermal Patch	0.025-0.1 mg per day
Estrace©	Micronized estradiol-17B	Oral	0.5 to 1mg per day
Estrace© cream	Micronized estradiol-17B	Topical	2mg per day
Estring©	Estradiol-17b ring	Vaginal Ring	2mg per 90 day
Ferming©	Estradiol acetate	Vaginal Ring	0.05mg per day
Osphena©	Ospemifene	Oral	60 mg per day
Premarin©	Conjugated estrogen	Oral	0.3 to 0.625 mg per day
Premarin© Vaginal	Conjugated estrogen	Topical	0.5 to 2 grams per day
Vagifem©	Estradiol	Vaginal Tablet	10 mcg per day
EvaMist©	Estradiol	Topical Spray	1.53mg per spray, 1-3 sprays daily



# Alternative Treatments: SSRIs/SNRIs

There are many reasons a patient is not able to take HRT including prescription contraindications, obesity, and cardiovascular risk. In the event a patient cannot take HRT, alternatives are available.

## SSRI and SNRI BACKGROUND FOR PROVIDERS

- While the most effective medication to manage vasomotor symptoms is systemic HRT, alternatives such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), and Clonidine have proven efficacy.
- SSRI and SNRIs begin working in about 2 weeks. Clinicians should start at the lowest dose for 2 weeks then may increase to standard dose.
  - To stop the drug, the lowest dose should be given for 2 weeks before discontinuing medication.
- Side effects of SSRI and SNRI use include nausea, asthenia, dizziness, xerostomia, constipation, and sexual dysfunction
- SNRI use warrants blood pressure monitoring as they can increase blood pressure.
- For SSRIs, Paroxetine, Citalopram, and Escitalopram have the best safety profiles.
- For patients with breast cancer on Tamoxifen, do not prescribe paroxetine and fluoxetine as they can decrease the active metabolite from Tamoxifen. Consider the use of SSRIs Citalopram and Escitalopram and SNRIs Venlafaxine and Desvenlafaxine.

## SSRIs for Hot Flashes and Mood Swings

Medication Name	Dose	Effectiveness
Paroxetine	10-25mg/day	May reduce up to 64% of hot flash symptoms and improve of sleep
Fluoxetine	10-30mg/day	May reduce up to 19% of hot flash symptoms
Sertraline	25-100mg/day	Modest effect on hot flashes
Citalopram	10-20mg/day	May reduce hot flashes by 23-50%
Escitalopram	10-20mg/day	Best tolerated effect on hot flash symptoms

## SNRIs for Hot Flashes and Mood Swings

*\*For patients diagnosed with breast cancer*

Medication Name	Dose	Effectiveness
Duloxetine	30-120 mg/day	56% and 62% reduction of hot flashes; moderate effect on CYP2D6 enzyme and safest choice
Venlafaxine	37.5-150 mg/day	Immediate effect and strong hot flash reduction of 30% to 58%; Lower effect on CYP2D6 and safest choice
Dexvenlafaxine	100-150 mg/day	May reduce up to 50% of hot flash symptoms



# Alternative Treatments: Herbal Therapies

*There are many reasons a patient is not able to take HRT, in which case alternatives are available. The following chart includes a provider guide for herbal therapies to address menopausal symptoms.*

## Herbal Therapies

Name	Background	Dose	Usage
Soy	Plant derived phytoestrogen and has similar properties to low dose estrogen therapy	<ul style="list-style-type: none"> <li>34-100 mg isoflavones (IS) for hot flashes</li> <li>50-118 mg of IS daily for 12 weeks for urogenital symptoms</li> <li>1 gram of soy extract 4% gel daily for 12 weeks for vaginal symptoms</li> <li>75-90 mg of IS can increase bone density</li> </ul>	<ul style="list-style-type: none"> <li>Decreases frequency and severity of hot flashes;</li> <li>Conflicting studies for BMD and vaginal symptoms</li> <li>Can lead to hypoglycemia and hypotension</li> </ul>
Equol	Chemically classified as a non-steroidal estrogen produced from soy isoflavones in the body as an intestinal bacterial metabolite which has estrogenic properties	<ul style="list-style-type: none"> <li>S-equol 10-30 mg daily for hot flashes and improved mood</li> </ul>	<ul style="list-style-type: none"> <li>May reduce the severity of vasomotor and genitourinary symptoms</li> <li>Data to support effectiveness /dosing is limited</li> </ul>
Equelle	Plant-based metabolite	<ul style="list-style-type: none"> <li>1-2 pills daily</li> <li>Takes 90 days before becoming effective</li> </ul>	<ul style="list-style-type: none"> <li>Reduce hot flashes</li> <li>Increase sleep, alleviate mood swings</li> <li>Relieves muscle aches, supports health bones</li> <li>Supports vascular health</li> </ul>
Purified Pollen Extract	Supplement sourced pure from pollen extract green climacteric combination of pollen and pistil extracts	<ul style="list-style-type: none"> <li>40mg of GC Fem, 120mg of PI 82 and 5 mg of vitamin E</li> </ul>	<ul style="list-style-type: none"> <li>Reduces vasomotor symptoms, mood swings, dizziness, tiredness, and insomnia</li> </ul>
Black Cohosh	Suggestive selective modulation of estrogen receptors (SERM) and antioxidant and anti-inflammatory effects	<ul style="list-style-type: none"> <li>20mg twice daily; Tincture form dose is 2 mL twice daily</li> <li>40-127mg daily for 12 weeks</li> </ul>	<ul style="list-style-type: none"> <li>Insufficient data to support use for controlling menopause symptoms</li> </ul>
Chasteberry	A shrub native to the Mediterranean and Central Asia	<ul style="list-style-type: none"> <li>15 mg twice daily for 8 weeks</li> </ul>	<ul style="list-style-type: none"> <li>Reduces anxiety and vasomotor functions by 76% and 88%</li> </ul>



# Alternative Treatments: Herbal Therapies

*There are many reasons a patient is not able to take HRT. In the event a patient cannot take HRT, alternatives are available. The following chart includes a provider guide for herbal therapies to address menopausal symptoms.*

## Herbal Therapies

Name	Background	Dose	Usage
Flaxseed (Linum Usitatissimum)	Common dietary source of fiber and omega-3 fatty acids and rich source of lignan phytoestrogens	<ul style="list-style-type: none"> <li>25-40grams daily dosing</li> </ul>	<ul style="list-style-type: none"> <li>Use as omega-3 fatty acids in diet but evidence does not support management of menopause</li> </ul>
Kudzu	Climbing vine native to Asia which contains isoflavones that have estrogenic and antiestrogenic activity similar to SERMs	<ul style="list-style-type: none"> <li>25mg, 50mg, or 100 mg daily for 6 months for vasomotor symptoms; may also improve flexible thinking and attention</li> <li>0.5 grams of gel contain Kudzu 6% for 11 weeks for vaginal symptoms</li> </ul>	<ul style="list-style-type: none"> <li>Does not improve sex hormone levels and may worsen lipid levels</li> <li>Does not improve vaginal symptoms when compared to conjugated estrogen cream</li> <li>Caution for patients on anticoagulant or antiplatelet therapy</li> </ul>
Ginseng	Panax ginseng is a root used in traditional Chinese medicine with estrogen like activity and may affect levels of dehydroepiandrosterone (DHEA) and testosterone	<ul style="list-style-type: none"> <li>1 gram three times daily for 12 weeks to reduce hot flashes</li> <li>Korean Red Ginseng 500 mg four times daily for two months improves fatigue</li> <li>Panax Ginseng 500 mg twice daily for four weeks may improve vaginal itching and burning</li> <li>Korean Red Ginseng 3 grams daily for two months modestly improved sexual arousal and satisfaction</li> </ul>	<ul style="list-style-type: none"> <li>Panax Ginseng may cause insomnia, has been associated with prolonging the QT interval in short term use and can modestly inhibit CYP2D6 enzyme, and modify the function of the CYP3A4 enzyme</li> <li>Panax Ginseng may decrease platelet aggregation or alter metabolism of warfarin</li> </ul>
Oxybutinin	Anticholinergic effect for hot flash reduction frequency and severity	<ul style="list-style-type: none"> <li>2.5mg twice daily or 5mg twice a day</li> </ul>	<ul style="list-style-type: none"> <li>Effective for hot flashes and can be used in both healthy women and cancer survivors</li> </ul>



# Alternative Treatments: Herbal Therapies

*There are many reasons a patient is not able to take HRT. In the event a patient cannot take HRT, alternatives are available. The following chart includes a provider guide for herbal therapies to address menopausal symptoms.*

## Herbal Therapies

Name	Background	Dose	Usage
Red Clover	Phytoestrogen, mimics estrogen in the body	<ul style="list-style-type: none"> <li>5 ounces/150ml for 12 weeks; 500mg tablets contains 40mg plant estrogens</li> </ul>	<ul style="list-style-type: none"> <li>Controversial results on menopausal symptoms in studies for bone mineral disease loss, hot flashes, and night sweats, increase in HDL</li> </ul>
Evening Primrose	Extracted from the seeds of evening primrose plant which increase prostaglandin	<ul style="list-style-type: none"> <li>Up to 6 grams daily for 1 year</li> </ul>	<ul style="list-style-type: none"> <li>NIH states not enough evidence for treatment of anxiety, hair loss, hot flashes, insomnia, joint pain, mood swings, night sweats, weight gain, vaginal dryness</li> </ul>
Valerian Root	A grass with phytoestrogenic components which may increase the gamma aminobutyric acid (GABA) chemicals	<ul style="list-style-type: none"> <li>200 to 600 mg up to three times per day for up to 4 to 8 weeks</li> </ul>	<ul style="list-style-type: none"> <li>Use for promotion of reduction Anxiety and improve sleep regimen</li> </ul>
St. John's Wort (Hypericum perforatum)	Plant native to Europe with yellow, star shaped flowers for antidepressant effects; modulates serotonin, dopamine, and norepinephrine and inhibit the reuptake of these chemicals	<ul style="list-style-type: none"> <li>900 mg daily for up to 16 weeks alone or in combination with herbs reduces frequency of hot flashes</li> </ul>	<ul style="list-style-type: none"> <li>Has significant impact on inducing CYP enzymes: 1A2, 2B6, 2C19, 2C9, and P-glycoprotein</li> </ul>
Relizen	Plant based formula	<ul style="list-style-type: none"> <li>2 tablets per day with or without food</li> </ul>	<ul style="list-style-type: none"> <li>Takes about 2 months of use before symptoms improve with daily use</li> </ul>



# Primary Ovarian Insufficiency (POI)

*The normal female menstrual cycle stops at approximately age 51-52. Menopause prior to the age of 40 would be considered premature ovarian insufficiency warranting further investigation.*

## PRIMARY OVARIAN INSUFFICIENCY

### Background

Primary ovarian insufficiency is declining ovarian function and reduced fertility due to premature decrease in initial follicle number, an increase in follicle destruction, or poor follicular response to gonadotropins in women younger than 40 years who have elevated follicle stimulation hormone levels (at least 30-40 mIU/mL) and amenorrhea.

### Symptoms

POI symptoms include vasomotor symptoms, urogenital atrophy, osteoporosis, and fracture, cardiovascular disease, loss of the menstrual cycle, and infertility.

### Rare Cases

1% of women can be affected and 90% of cases are idiopathic, a small amount relate to a genetic or molecular derangements, and a few can be attributable to autoimmune disorders, single gene defects, and women who experience cancer diagnosis in which they require chemotherapy or pelvic radiation can also be at risk.

## PRIMARY OVARIAN INSUFFICIENCY TREATMENT CONSIDERATIONS

- Systemic HRT should be used to treat hypoestrogenism and mitigate long-term health risks.
- HRT can reduce the risk of osteoporosis, cardiovascular disease, and urogenital atrophy and can significantly improve a patient's quality of life.
- HRT should include the use of oral or transdermal estrogen and should achieve replacement/physiologic levels of estrogen. The addition of cyclic progesterone for 10-12 days each month is protective against endometrial hyperplasia and endometrial cancer, risks of unopposed estrogen.
- Oral estradiol may be used, but it increases the potential for thromboembolism relative to transdermal estradiol due to the first-pass effect on the liver.
- Oral contraceptives contain higher doses of estrogen than necessary for hormonal therapy; therefore, they are not recommended as first-line hormonal therapy.
- Higher dose hormone replacement or birth control options may be transitioned at the usual timing of menopause to a lower HRT dosing.
- In patients with decreased ovarian reserve or have sporadic fertility, hormone replacement via effective contraceptive is advised to avoid unintended pregnancy.



# HRT for POI

*Menopause prior to the age of 40 would be considered premature ovarian insufficiency warranting treatment with the options below.*

## Estrogen HRT for POI

Name	Route	Dose
Micronized 17B-Estradiol	Oral	1-2mg Daily
17B-Estradiol (Vivelle)	Transdermal	1 Patch Twice Weekly
Conjugated Equine Estrogen	Oral	0.625-1.25mg Daily

## Progesterone HRT for POI

Name	Continuous	Sequential
Medroxy-progesterone	2.5-5mg Daily	10mg for 12 days each month
Micronized Progesterone	100mg Daily	200mg for 12 days each month



# Testosterone

*Testosterone may be used to reduce sexual health symptoms for menopausal and post-menopausal women. It is most efficacious in conjunction with other HRT.*

**BACKGROUND** | Testosterone levels decrease over the years for women as they age. The lowest point of testosterone is often reached by women in their 60s and then it rises to premenopausal levels for women in their 70s.

- Testosterone can be used for postmenopausal women for decreases sex drive after other potential health concerns and relationship issues have been excluded.
- Testosterone can be added to HRT therapy as studies show positive response to the decreased sex drive symptomology noted with menopause and it does not address all other symptoms associated with menopause.

**INDICATION** | Testosterone therapy is not indicated for hormone replacement alone in postmenopausal women. Androgen therapy is specifically indicated for hypoactive sexual desire disorder, sexual arousal disorder, hypoactive sexual disorder, and other associated disorders. Androgen has not been shown to be effective for sexual dysfunction symptoms and therefore not recommended for use in these circumstances.

**SAFETY** | Adverse effects associated with testosterone therapy in women are hirsutism, acne, and virilization (including voice deepening and clitoral enlargement) especially at larger doses. When using transdermal formulation there is no demonstrated increased risk for cardiovascular events.

When initiating testosterone use, measure testosterone levels at baseline and at 3 to 6 weeks with initiation. Assess for signs of serum androgen excess through total testosterone level at every 6 months. If no response to therapy in 6 months, discontinue therapy.

**ROUTE OF MEDICATION** | Available formulations for use in women include patch, cream, ointment, or gel. These formulations can easily be titrated to the most effective dose with least side effects.

## Testosterone (T) Treatment

Name	Formulary	Dose	Length
Testogel	1% T gel in 5.0 gram sachets containing 50mg T	1/10 of a sachet/day = 5mg/day	Each sachet should last 10 days
Tostran	2% T gel in a canister containing 60 grams T	1 dose metered pump of 0.5-10mg	Provide on alternate days and canister should last 240 grams
AndroFeme	1% T cream in 50ml tubes with screw cap	0.5ml/day = 5mg/day	Each tube should last 100 days
Intrarosa	Active ingredient is Prasterone (Similar to DHEA). 6.5mg per insert/Suppository	6.5mg insert placed nightly	Medication used nightly continuously



# References

*Please find references and citations for clinical information contained in this guide.*

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