Menopause

Patient Management Guide

The Consilient Health Menopause Patient Management Guide has been developed in conjunction with Dr Caoimhe Hartley and Dr Deirdre Lundy.

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Menopause

Patient Management Guide

This guide is based on recommendations supported by the **British Menopause Society** and the **International Menopause Society** (although many other excellent resources exist).[1, 2] **Menopause Hormone Therapy** or **MHT** is fast regaining its popularity in Ireland as one of the many ways we can help relieve some of the symptoms of the Menopause.

Use of **MHT** has a limited risk profile when compared to other types of oestrogen+progestogen medications (specifically the combined hormone pills, patch and ring). **MHT** medications contain physiological types of oestrogens, progestogens (+/- androgens) and usually contain very small doses. As with all medications, there are some risks so this flip chart hopes to provide support and reassurance to **MHT** advisors, prescribers and their patients.

Definitions and Abbreviations

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Definitions

Perimenopausal is the time leading up to a woman's final period. There is variability in the menstrual cycle +/- vasomotor symptoms. The typical age of onset is from 45 years onwards but some women experience symptoms earlier.
Early Menopause is defined as a menopause between 40 and 45 years and occurs in about 5% of women.
Premature Ovarian Insufficiency (POI) is when FSH levels measure in the postmenopausal range in a person under 40 years. It affects about 1% of women.

Abbreviations

AI Aromatase Inhibitor
BMI Body Mass Index
BMS British Menopause Society
BP Blood Pressure
BSO Bilateral Salpingo Oophorectomy
BV Bacterial Vaginosis
CHC Combined Hormonal Contraception
CVA Cerebral Vascular Attack
CVD Cardiovascular Disease
DEXA / DXA Dual-Energy X-ray Absorptiometry / Bone Density Scan
DHEA Dehydroepiandrosterone
DYDRG Dydrogesterone
FBC Full Blood Count
FSH Follicle Stimulating Hormone
GMS / GUSM Genito-urinary Syndrome of the Menopause. This is the new term for vulvo-vaginal atrophy
HBA1C HbA1c is known as glycated haemoglobin. It is made when the glucose (sugar) in your body sticks to your red blood cells. A high HbA1c level means you have too much glucose in your blood
HRT Hormone Replacement Therapy
IM MPA Intramuscular Medroxyprogesterone Acetate
IMS International Menopause Society
IUB Intrauterine Ball
IUS Intrauterine System
LMP Last Menstrual Period
LNG-IUS Levonorgestrel Releasing Intrauterine Device
MHT Menopause Hormone Therapy
MI Myocardial Infarction
MP Micronised Progesterone
NET Norethisterone
NKB/NK3R Neurokinin B/ neurokinin-3-receptor
OAB Overactive Bladder
PCOS Polystic Ovarian Syndrome
PHQ-9 SCORE The Patient Health Questionnaire is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression[3]
PO Per oral
POI Premature Ovarian Insufficiency
POP Progestogen Only Pill
QOL Quality Of Life
SI Sexual Intercourse
SSRI Selective Serotonin Re-uptake Inhibitor
SNRI Serotonin Noradrenaline Re-uptake Inhibitor
TD Transdermal
TIA Transient Ischemic Attack
TSH Thyroid Stimulating Hormone
UTI Urinary Tract Infection
VMS Vasomotor Symptoms
VTE Venous Thromboembolism

Consultation Checklist: First Appointment[3,4]

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Diagnosis	• Last Menstrual Period • Assess bleeding pattern and impact on QOL, menopausal status • Consider using FSH level to diagnose menopause in women aged <45 with a change in menstrual cycle. • Consider TSH / FBC / Ferritin / Coeliac screening etc. to rule out potential causes of symptoms.
Consider using symptom checker to assess: See Symptom Checker on consilienthealth.ie	• Physical symptoms • Genitourinary symptoms • Mood, Emotional symptoms
Past Medical History	• Current medications • Thyroid • Migraines • Hypertension • Diabetes • Endometriosis
Past Surgical History	Hysterectomy / Oopherectomy / Blood clots
Past Gynaecological History	NB. Consider Contraceptive requirement
Family History	• History of Breast Cancer/ Gynaecological Cancer • VTE
Smoking / Vaping Status / Alcohol intake screening	Number / Units per day
Screening	Cervical Smear / Mammogram / DEXA
Physical Exam	• Examine women where indicated by history • Blood Pressure / BMI Mandatory All else at discretion of clinician if indicated by complaints.
Other	In addition to using a symptom checker, as outlined above, where relevant consider using the PHQ9 Questionnaire to monitor severity of depression - available on the www.patient.info website[3]

Consultation Checklist: Patient Management

Consultation: Discussion re Management Options[4,5,6,33]

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Discuss options including; Lifestyle Interventions, Hormonal Options, Non-Hormonal Options, Contraceptive Options and Vaginal Moisturisers / Lubricants/Localised Oestrogen.

- Discuss potential risks and side effects including breast tenderness, headaches, bloating
- Explain that unscheduled or irregular bleeding can be common in the first 3-6 months after starting HRT[5]
- Combination HRT (oestrogen and progestogen) necessary for women with an intact uterus either as cyclical / sequential (for perimenopausal women) or continuous HRT (for postmenopausal women).
- Oestrogen alone can be prescribed for women who have had a hysterectomy. However combination HRT (oestrogen and progestogen) may be indicated for hysterectomised women with a history of endometriosis.

Risks: VTE and / or stroke risk increased with oral HRT compared to population risk. No increased risk associated with low dose transdermal preparations. Consider transdermal rather than oral oestrogen for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m2/ women who have a history of migraine, smoking, diabetes etc.

Breast Cancer: Baseline risk is dependent on individual factors including family history and lifestyle. According to the Women's Health Initiative clinical trials, HRT with oestrogen alone is associated with little or no change in breast cancer risk[38]. HRT with oestrogen and progestogen combined may be associated with an increased risk of breast cancer which is dependent on the type of progestogen used and duration of use[6]. According to the ICGP a review is recommended three months after commencing HRT and annually thereafter unless a sooner review is clinically indicated (e.g. side effects, inadequate effectiveness, adverse event).

Benefits: HRT is the most effective therapy for symptom control including vasomotor symptoms, joint and muscle pains, mood changes and sleep disturbances. It provides a reduction in cardiovascular disease for women aged < 60 and within 10 years of their LMP, and a significant reduction in osteoporosis.[4]

Consultation: Discussion re Management Options

Consultation Checklist: Review Appointment

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- Review response to treatment and any current symptoms
- Assess bleeding status/ pattern of bleeding
- Blood pressure
- Review risks and benefits of current management plan
- Review screening status
- Advise no arbitrary limits with regards to HRT use

Consultation Checklist: Review Appointment

Prescribing Guide – HRT Medicines[7,8,9,33,36,37]

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Oestrogen

Oral:

- **Estrofem** 2mg daily (estradiol)
- **Fematab** 1mg - 2mg daily (estradiol)
- **Premarin** 0.625mg PO daily (Conjugated estrogens)

Transdermal:

- **Divigel Transdermal Gel** 0.1% gel: starting dose 0.5mg estradiol (half a sachet) daily to skin of the lower trunk or the thigh.
- **Estradot Transdermal Patch** 25mcg/ 37.5mcg/ 50mcg/ 75mcg/ 100mcg estradiol per 24 hours. Patches should be applied to the abdomen below the waist
- **Evorel 50 Transdermal Patch** 50mcg estradiol per 24 hours.[36] Patches should be applied below the waist.
- **Lenzetto Transdermal Spray** 1.53mg estradiol 1-3 sprays daily to the forearm
- **Oestrogel Transdermal Gel** Starting dose 1-2 pumps (0.75mg - 1.5mg estradiol) once a day. Apply to the skin of the arms / shoulders or inner thigh daily.

Advice given is based on the experience of practitioners working in this area. Advice for Evorel 50 is as per SPC. Please refer to the relevant SPC for all other medicines.

Prescribing Guide – HRT Medicines

Prescribing Guide – HRT Medicines[7,8,9,10,25,33,36,37*]

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Progestogen - doses outlined below are for women who are using ≤ 50mcg Oestrogen

Bleed Producing/Sequential*:

- **Duphaston** Dydrogesterone: 10mg- 20mg PO daily x 12-14 days per cycle.
- **Utrogestan** Micronised Progesterone 100mg capsules. Recommended dose 200mg nocte PO for 12-14 days per cycle.[25]
- **Provera** Medroxyprogesterone Acetate: 10mg-15mg PO x 12-14 days per cycle.

No Bleed/Continuous*:

- **Duphaston** Dydrogesterone: 10mg - 20mg PO daily.
- **Utrogestan** Micronised Progesterone 100mg capsules. Recommended dose 100mg nocte PO.[25]
- **Mirena** Intrauterine Device Levonorgestrel - provides 5 years of endometrial protection - 52mg IUCD with (in most cases) limited systemic side effects.
- **Provera** Medroxyprogesterone Acetate: 2.5- 5.0mg PO daily.

Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

Note: Guidance from the BMS states that "The dose of the progestogen should be proportionate to the dose of oestrogen" [33] All of these sequential progestogen doses are based on standard low dose oestrogen of 50 mcg or less. Over 50 mcg oestrogen will require additional progestogen.[25]

*Other progestogens / other doses of micronised progesterone are also available as Exempt Medicinal Products, information on the supply of these medicines can be provided from the manufacturer. Further information on Exempt Medicinal Products can also be found on the HPRA website, www.hpra.ie

Prescribing Guide – HRT Medicines

Prescribing Guide – HRT Medicines[7,8,9,10,25,33,36,37*]

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Progestogen - doses outlined below are for women on higher doses of oestrogen

Bleed Producing / Sequential*:

Any 75-100mcg Oestrogen equivalent &

- **Utrogestan** Micronised Progesterone (100mg capsules): Recommended dose 300mg nocte PO, for 12 - 14 days per cycle.[25]
- **Duphaston** Dydrogesterone: 30mg for 12- 14 days/ month
- **Provera** Medroxyprogesterone Acetate: 5mg for 12- 14 days/ month
- **Mirena** Intrauterine Device Levonorgestrel: 5 years only

Non-Bleed / Continuous*:

Any 75- 100mcg Oestrogen equivalent &

- **Utrogestan** Micronised Progesterone (100mg capsules): 200mg nocte PO[25]
- **Provera** Medroxyprogesterone Acetate: 2.5mg/day
- **Duphaston** Dydrogesterone: 20mg daily
- **Mirena** Intrauterine Device Levonorgestrel: 5 years only

Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

Note: Guidance from the BMS states that "The dose of the progestogen should be proportionate to the dose of Oestrogen" [33] Over 50 mcg Oestrogen will require additional progestogen. [25]

*Other progestogens / other doses of micronised progesterone are also available as Exempt Medicinal Products information on the supply of these medicines can be provided from the manufacturer. Further information on Exempt Medicinal Products can also be found on the HPRA website, www.HPRA.ie

Prescribing Guide – HRT Medicines

Prescribing Guide – HRT Medicines[7,8,9,33,36,37]

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Combination Products

Bleed Producing/Sequential:

- **Femoston** Estradiol 1mg/2mg only x 14 tabs followed by Estradiol 1mg/2mg and Dydrogesterone 10mg x 14 tabs
- **Novofem** Estradiol 1mg only x 16 tabs followed by Estradiol 1mg and Norethisterone acetate 1mg x 12 tabs
- **Trisequens** Estradiol 2mg only tabs x 12 days followed by Estradiol 2mg and Norethisterone acetate 1mg tabs x 10 days followed by Estradiol 1mg tabs x 6 days

No bleed/Continuous:

Oral:

- **Activelle** Estradiol 1mg and norethisterone acetate 0.5mg PO daily
- **Kliogest** Estradiol 2 mg and norethisterone acetate 1mg
- **Angeliq** Estradiol 1mg and 2 mg drospirenone
- **Femoston Conti** Estradiol and dydrogesterone 0.5mg/2.5mg or 1mg/5mg

Tibolone: Synthetic steroid compound. Has oestrogenic/ progestogenic /weakly androgenic effects. Do not need to add progestogen for endometrial protection.

Indivina: Estradiol valerate and medroxyprogesterone acetate. 1mg/2.5mg, 1mg/5mg and 2mg/5mg, 1 tablet daily. Replacement therapy for oestrogen deficiency in women more than three years after menopause with an intact uterus.

Transdermal Patch:

- **Evorel Conti** Estradiol 50mcg and Norethisterone acetate 170mcg/ 24 hours.[37] Patches should be applied below the waist.

Advice given is based on the experience of practitioners working in this area. Advice for Evorel Conti is as per SPC. Please refer to the relevant SPC for all other medicines.

Prescribing Guide – HRT Medicines

Prescribing Guide: Non-HRT Options [17, 31]

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Managing menopause symptoms without HRT - for some people, non HRT therapies and products are a better fit

Not everyone is going to want or need HRT and some have been advised to avoid HRT. Most women will cope with their menopause symptoms on their own without involving their GP, for some people, non HRT therapies and products are a better fit.

1. Food and dietary supplements

Vitamins & Minerals

A balanced healthy diet is the ideal way to maintain good health through the menopause. If you have to avoid certain foods and worry you are not taking in enough vitamins or minerals, then an inexpensive multivitamin is a good idea. In Ireland, some supplemental vitamin D is advised as we do not get enough ambient sunshine – especially in the winter.

Herbal Products[31]:

Black Cohosh - The BMS say that while some studies do show Black Cohosh can help relieve vasomotor flushes and sweats, it is also associated with side effects (such as constipation, stomach cramps, heart rhythm disorders, weight gain) but most importantly, it interferes with the breast cancer drug 'Tamoxifen' and so must not be used in people using that medicine.

St John's Wort - Classified as Prescription Only in Ireland. It has been shown to be effective for both menopausal flushing and low mood. It may impair the activity of other medications as it is a liver enzyme inducing drug. So people on certain cancer drugs, hormonal contraception, HRT, etc. need to avoid it. Women who are being treated for breast cancer with Tamoxifen must not take St John's Wort.

Ginseng - The BMS say Ginseng and Chinese herbal medicines have not been shown to improve hot flushes, anxiety or low mood.

Isoflavones - Found in legumes such as soybeans, chickpeas and tofu. The BMS says "Most studies evaluating effectiveness of phytoestrogens are of poor quality and were not shown to reduce hot flush frequency. Data on phytoestrogen safety and survival benefits in breast cancer patients are inconsistent and as they are known to have oestrogenic activities, isoflavones including Red Clover are not recommended for breast cancer survivors."

Wild yam, Red clover, Dong quai, Gingko, Sage, Maca, Pollen extract, Vitamin E, Evening primrose Oil: No evidence to show they help with menopausal symptoms.

Prescribing Guide: Non-HRT Options [17, 31]

2. Physical/Psychological therapies and treatments

Avoiding heat triggers - hot tea and coffee, spicy foods, alcohol might launch a flush. Other common triggers include smoking, stress, exercise, and many more.

Environmental adjustments - keeping your environment cool (especially in the bed at night), wearing light layered clothing, electric fans, using ice packs or cooling packs. There are also benefits to reducing alcohol and caffeine.

Smoking cessation - ask your GP to get involved in helping you reduce or stop smoking.

Behavioural therapies - **Cognitive Behavioural Therapy (CBT)** which combines relaxation techniques, sleep hygiene and learning to take a positive healthy attitude to menopause is also recommended. It can be offered too as a treatment for anxiety related to menopause. CBT can have an impact on both vasomotor symptoms, perception & control.

Acupuncture/ acupressure for menopause - is probably quite safe when done by a well-trained practitioner but sadly has not been shown to relieve menopause symptoms, meaning any improvement may be placebo.

Yoga for menopause - there is no robust scientific evidence to prove that yoga specifically helps with flushes / sweats / mood etc. Many people gain enormous relief and pleasure from yoga. It can be a nice form of exercise and we know gentle exercise is good for so many medical complaints.

Massage - there are no large-scale clinical trials specifically looking at massage for menopause symptoms and comparing it to other menopause treatment options.

Vaginal Lasers for GSM - There is emerging evidence for the use of LASER therapy- particularly cold, Erbium LASER treatment as opposed to warm, CO2 LASER therapy in treatment of GUSM/GSM. They are available in Ireland but can be expensive and clinical evidence for their use is lacking. Further studies on the use of local vaginal LASER for GSM are required.
Prof Tom Hilliard et al stated that Vaginal Erbium Laser may be considered for Post Menopausal women with a history of breast cancer.

Vaginal Moisturisers and Lubricants - May help improve the symptoms of vaginal dryness and discomfort.

3. Prescription Medications[1,31,32,33]

A. Clonidine: An adrenergic receptor agonist licensed in Ireland for the treatment of hypertension and menopause symptom control (hot flushes). Dose is 25mcg BD for 2 weeks, increased up to a maximum of 50mcg TID. One study showed significant reduction in the numbers of flushes + improved QoL compared with placebo in breast cancer survivors using 100mcg daily. Side effects of clonidine are dose related- at higher doses it causes sleep disturbance in >50 % of users. It must be withdrawn gradually as abrupt cessation can cause rebound hypertension. Clonidine obviously may not be suitable for patients with a baseline low blood pressure.

B. Selective Serotonin re-uptake inhibitors (SSRI) and the Serotonin Noradrenaline re-uptake inhibitor/selective Serotonin re-uptake inhibitors (SSRI-SNRI) are normally used for depression and anxiety but in the USA, the FDA approved Paroxetine for menopausal hot flushes. Venlafaxine 37.5mg titrated up to 150mg per day, Paroxetine 10mg daily or Citalopram 10mg-30mg are the most effective according to the BMS consensus statement [31]. Fluoxetine has evidence of efficacy and lower incidence of side effects. Sertraline seems least effective. Escitalopram improves flushes and has significant benefits and improvement in wellbeing but some side effects. Side effects include dry mouth, nausea, constipation - dose related. Reduced libido is a class effect.

Some SSRIs inhibit cytochrome P450 activity which is involved in Tamoxifen metabolism so most guidelines recommend that SSRIs such as Fluoxetine and Paroxetine must not be prescribed concomitantly with Tamoxifen. So, as **Paroxetine 10mg** is the SSRI with the best evidence for efficacy (although 20 mg may be used if an antidepressant effect is also required), it is the SSRI of choice for patients not taking Tamoxifen. **Venlafaxine 75mg is the preferred treatment for breast cancer survivors taking Tamoxifen.**

C. Gabapentin is an anti-epileptic medicine but 300mg daily increasing to 300mg TDS OR Pregabalin 75-150mg BD shows significant improvement in hot flushes as compared with placebo according to the BMS. It is recommended to start patients on a sub therapeutic dose of 100mg to avoid side effects. Dose dependent side effects may affect compliance, the most common side effects being somnolence, dizziness, weight gain and dry mouth. Gabapentin may be as effective as Venlafaxine. Pregabalin is licenced for depression.

Note: It is not recommended to use the above medications in conjunction with one another

Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

Prescribing Guide: Non-HRT Options [1,31,32,33,36,37,41]

D. Oxybutynin is an anticholinergic medication for urinary incontinence/ overactive bladder when taken 2.5 mg or 5 mg BD appears to be effective in the treatment of hot flushes in menopause including breast cancer survivors – trials are underway in the USA. Possible side effects include dry mouth or eyes, headache, dizziness, vertigo, GI upset, dry eyes.

E. The future - **Neurokinin receptor 3 antagonists** demonstrate a rapid effect on vasomotor symptoms but can be offered to people with Oestrogen dependent cancers – results of trials are due in 2023. Neurokinin B/ neurokinin-3-receptor (NKB/NK3R) is involved in the pathways that allow the development of hot flushes, interacting with the temperature controlling centre in the brain. Therefore, agents which act against neurokinin-3-receptor (NK3R antagonists) could suppress the pathway and reduce flushes and sweats. One such antagonist, **NT-814**, has shown promising results. A study showed that NT-814 significantly reduces hot flush frequency, improves sleep, mood, and quality of life with no safety concerns.[32]
Further studies are required and are underway, but the possibility of an effective, safe non-hormonal option for women who cannot, or prefer not to take HRT is an exciting prospect for the future.

Compounded Bioidentical and Regulated Bioidentical Hormone Replacement Therapy[41]
These are hormone-containing pellets, creams or pessaries that are produced in private laboratories.
Compounded Bioidentical Hormone Replacement Therapy (cBHRT): Precise duplicates of human hormones which are produced by specialist pharmacies and do not follow the same regulatory pathway as conventional rBHRT.
Regulated Bioidentical Hormone Replacement Therapy (rBHRT): Precise duplicates of human hormones developed in a conventional way by the pharmaceutical industry and authorised by the regulators. [41]

Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

Treatment of Genitourinary Syndrome of the Menopause[11,12,13,14,15]

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Symptoms linked to declining systemic oestrogen levels, oestrogen receptor numbers and pelvic floor vasculature include- Thinning of both muscularity and epithelium (with an increase in fat deposition) resulting in…

- Altered PH with an increased potential for BV and other infections
- Traumatic Bleeding after SI or PV exams
- Vaginal dryness
- Vaginal burning & irritation
- Sexual symptoms such as lack of lubrication & Dyspareunia
- Urinary symptoms such as: Urgency, Frequency, Dysuria & recurrent UTIs.

First Line Treatments - Non Rx Medical Therapies

Most Menopause societies suggest patients should at least try non Rx medical therapies such as:

- Vaginal moisturisers which maintain vaginal hydration, long-term relief of vaginal dryness, decreased pH to premenopausal levels but – these do not improve epithelium (examples include- Replens, Regelle, Multi-gyn, Yes, etc)
- Vaginal lubricants which provide a temporary moistened vaginal epithelium. May be water, silicone or oil based (KY, Sylk, Yes, etc)
- Herbal remedies (soy, black cohosh, etc) have not been shown effective over placebo.[15]

When these are not adequate, Prescription GSM remedies are recommended.

Treatment of Genitourinary Syndrome of the Menopause

Treatment of Genitourinary Syndrome of the Menopause [7,11,12,13,14,15,36,37]

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Second Line Treatments - Local Vaginal Oestrogen

Symptoms usually respond very well to local vaginal oestrogen containing products. These generally do not enter the systemic circulation in any meaningful way and can be offered to almost all patients including patients for whom systemic HRT is contraindicated e.g. patients who have been diagnosed with breast cancer. There are some considerations though.

These include-

- Local Oestrogen will thicken the epithelium, decrease dryness, return vaginal pH to normal and improve microflora with fewer UTI and decreased OAB symptoms.
- Systemic oestrogen (HRT) may also help GSM patients, but they will often need both systemic & local therapy although there may be adherence issues; studies suggest just 50-70% take as recommended!.
- Dosing in MIMS is not aligned with Menopause society guidelines – and 4-6months to see full results so perseverance is needed.
- Side effects can include local irritation – this may be due to a sensitivity to the hormone or the excipients but is often because the damaged vulvo vaginal tissues are acutely sensitive to any and all products, should ease with continued use.
- Provides virtually no systemic effect apart from a brief rise when applied to an atrophic vagina – so don't stop/start treatment. Refer to oncology or an accredited menopause specialist for people on Aromatase Inhibitors.
- No impact on endometrium, opposing progestogen not required.

Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

Treatment of Genitourinary Syndrome of the Menopause

Treatment of Genitourinary Syndrome of the Menopause [7,11,12,13,14,15,36,37]

Consilient Health

Treatments licensed for post-menopausal patients (Also useful for Premature Ovarian Insufficiency, Early Menopause and Perimenopause).

Blissel[42]	1 g vaginal gel contains 50 micrograms Estriol.	Treatment of symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women.	Initial treatment: One applicator-dose of vaginal gel per day for 3 weeks. Maintenance treatment one applicator-dose of vaginal gel twice a week.	Vaginal Gel with Applicator
Imvaggis (E3)	Oestrogen / Estriol 0.03mg	Treatment of vaginal symptoms of oestrogen deficiency in post-menopausal women.	Initial Dose: 1 daily for 3 weeks Maintenance Dose: 1 twice a week	Pessary
Ovestin	Vaginal cream containing 1 mg Estriol	Treatment of symptoms of vaginal atrophy due to oestrogen deficiency in post-menopausal women.	Initial Dose: 1 application daily for up to 4 weeks, followed by a gradual reduction. Maintenance dosage: 1 application twice a week	Vaginal cream with applicator
Vagifem	Oestrogen / Estradiol 10 mcg	Vaginal atrophy due to oestrogen deficiency in post-menopausal women.	Initial Dose: 1 daily for 2 weeks Maintenance Dose: 1 twice a week	Vaginal Tablet (with individual applicators)
Vagirux	Oestrogen / Estradiol 10mcg	Treatment of vaginal atrophy due to oestrogen deficiency in post-menopausal women.	Initial dose: 1 daily for two weeks Maintenance dose: 1 twice a week	Vaginal Tablet (with a single reusable applicator)

Advice given is based on the experience of practitioners working in this area. Advice for Blissel is as per SPC. Please refer to the relevant SPC for all other medicines.

Treatment of Genitourinary Syndrome of the Menopause

Treatment of Genitourinary Syndrome of the Menopause[10,36,37,39]

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Non-Oestrogen Prescription GSM therapies[10]

Prasterone (A DHEA cream approved in the USA for use in Non Oestrogen Receptor Positive Breast Cancer Patients with vaginal symptoms after breast cancer.) and **Ospemifene** (An Oral GSM medicine) are available as Exempt Medicinal Products, information on the supply of these medicines can be provided from the manufacturer. Further information on Exempt Medicinal Products can also be found on the HPRA website, www.HPRA.ie [10]

Non-Medical GSM therapies

1. **Fractional CO2 delivered by apparatus**: One course of laser treatment includes two or three laser sessions at an interval of approximately 4 ± 1 weeks[39]. Annual maintenance is needed. The heat increases blood flow, collagen production & vaginal epithelial regrowth. No need for LA nor recovery time but local burning not uncommon. So this has mostly been replaced by Erbium laser treatment.

2. **Erbium Laser Rejuvenation** with brand names such as "Fotona Smooth" & "IntimaLase" are alternative LASER therapies to fractional CO2. They are associated with less risk of local burning as erbium is a cold LASER.

Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

Treatment of Genitourinary Syndrome of the Menopause

Testosterone[16,17,18]

Note: Testosterone is currently not licenced in Ireland for use in women in the treatment of menopause.

Testosterone is an important female hormone and is primarily produced by the ovaries and the adrenal glands.

Testosterone concentrations fall during the reproductive years. Loss of testosterone is particularly profound after early surgical and medical menopause and premature ovarian insufficiency when testosterone production decreases by more than 50%.

There is no cut-off blood level which can differentiate women with or without sexual dysfunction.

Indications:

- The only evidence-based indication for the use of testosterone in women is for the treatment of postmenopausal women who have been diagnosed as having hypoactive sexual desire disorder (HSDD).[16]
- Testosterone therapy in doses that approximate physiological levels for premenopausal women may exert a benefit on sexual function.[17]

What to prescribe:

- It is not recommended to prescribe any testosterone preparation that results in supraphysiologic concentrations of testosterone.
- With any prescription of testosterone, levels should be maintained in the normal female range.

From the BMS:

Compounded bioidentical testosterone preparations are not recommended by the regulatory authorities or the menopause societies.

Direct assays for the measurement of total and free testosterone are highly unreliable in the female range and are technically difficult.

Baseline total testosterone concentration should be measured before commencement, with a repeat level 6-12 weeks after treatment initiation. Patients should be monitored with a serum total testosterone level +/- free androgen index every 6 months. If no benefit is achieved after 6 months, treatment should be stopped.

Also see troubleshooting section re. testosterone related side effects

Troubleshooting: Oestrogen Risk[1,6,9,11,19,36,37]

VTE "the risk of venous thromboembolism (VTE) is increased by use of an oral oestrogen containing HRT product compared with baseline population risk, the risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline population risk". NICE

VTE Side Effects

ACTION

- Advise patients that there is 2-4x increased risk of VTE when starting oral oestrogen HRT.
- Risk of VTE with oral HRT use is highest in the first year.
- Advise patients that there is no increased risk with transdermal oestrogen when used in standard doses.
- HRT is not contraindicated, but a non-oral route is preferred in patients at higher risk of VTE such as: patients over 60 years, patients with a BMI > 30, patients with a personal history of VTE, patients with a strong family history of VTE, patients undergoing immobilisation or surgery etc.
- Norpregnane derivative progestogens (Nomegestrol and Norethisterone*) and particularly Medroxy Progesterone Acetate (Provera) are not recommended in patients with increased VTE potential.
  Prescribers should consider micronised progesterone, dydrogesterone or a levonogestrel intrauterine device for women at high risk of VTE
  *This is based on studies using oral norethisterone in the hormonal contraceptive pill as opposed to transdermal norethisterone. Available evidence from studies of the contraceptive pill suggests that transdermal administration may have a lower risk[19].

For patients with a personal history of VTE, HRT use should be discussed with their Haematologist and a prescriber with Menopause training.
Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

CARDIOVASCULAR DISEASE

Troubleshooting: Oestrogen Risk[1,6,19,36,37 *]

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Cardiovascular Disease "the presence of cardiovascular risk factors is not a contraindication to HRT as long as they are optimally managed." NICE

"The risk of developing cardiovascular disease is not increased by use of HRT when started in women aged under 60 years." NICE

Cardiovascular Disease Side Effects

ACTION

There is no reliable evidence linking the use of HRT to cardiovascular disease in women under 65 years. HRT can be offered to women with cardiovascular risk factors once those risks have been optimally managed.

Advise patients that many forms of HRT have a beneficial effect on lipids, vascular function, and sugar metabolism.

Data supports the concept of primary prevention of coronary vascular disease and CVD mortality when HRT is started in women under 60 years of age and within 10 years of their final period.

For patients with established CVD: HRT use should be discussed with their Cardiologist / Prescriber with Menopause training. HRT has been generally contraindicated but more recent data suggests that in women with a past history of MI who are being well managed and are stable, the cautious use of low dose transdermal oestrogen (<50 mcg) and micronised progesterone is acceptable.

The BMS experts have also advised members that peripheral vascular disease is only a special caution for HRT - not an absolute contraindication- but obviously avoid PO routes.

Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

Troubleshooting: Oestrogen Risk[1,6,19,20,36,37 *]

STROKE

Stroke "the use of oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke but the baseline risk for women under 60 years is low." NICE

"HRT should not be recommended for the primary or secondary prevention of stroke, low dose (50mcg/day) TD oestrogen was not linked to an increased risk of Stroke, in patients under 60 who had been prescribed HRT. Higher dose TD oestrogen and oral oestrogen HRT were associated with an increased risk of stroke so exercise caution when prescribing for people with Stroke risk including patients over 60 years of age.

Progesterone type may have an impact on the risk of ischemic stroke. A French study showed a link between ischemic stroke and the use of HRT with norpregnane derivative progestogens (Norethisterone and Norgestrel) but not with the use of micronised progesterone (Utrogestan) or dydrogesterone (Duphaston)[20].

Stroke side effects

ACTION

- Advise patients that the use of low dose (50mcg/day) TD oestrogen was not linked to an increased risk of Stroke, but higher dose TD HRT and oral HRT may increase stroke risk- particularly ischemic stroke (with no effect on haemorrhagic stroke).
- Advise patients that the use of Micronised progesterone and Dydrogesterone are preferred for people with risk factors for stroke. People with stroke risk factors should have their modifiable risks managed before commencing HRT.
- Patients with a past history of stroke are generally advised to avoid HRT (particularly oral oestrogen products) or to discuss options with a menopause specialist.

Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

Troubleshooting: Oestrogen Risk*[6,19,21-24,28,33,40]

Consilient Health

General Comments

Breast cancer The most commonly occuring female cancer in Ireland. One in nine women will develop breast cancer in their lifetime.[40]

- Breast cancer prognosis continues to improve.
- Several factors influence breast cancer risk including age, family history, parity, BMI, smoking, alcohol consumption etc.

Hormone Replacement Therapy

- Current evidence suggests that Oestrogen-only therapy is associated with little or no increase in the risk of breast cancer.[38]
- There is an increased risk of breast cancer with combined HRT which is duration dependent. Risk varies depending on the type of progestogen used.[6,19] The overall impact on risk with combination therapy is small in statistical terms when compared with modifiable lifestyle factors including alcohol. The chart on the next page can be useful when explaining the risk to a patient.
- For the majority of women, benefits of HRT in the short-term (up to five years) for symptom relief will exceed potential harm with overall reductions in all-cause mortality.
- Large observational data suggests that micronised progesterone and dydrogesterone are likely to be associated with a lower risk of invasive breast cancer when compared to other progestogens.
- There is no difference in breast cancer risk with oral versus transdermal oestrogen.
- Increasing doses of oestrogen do not appear to confer higher risk.[21]
- Mammogram and breast cancer screening can be continued as per local guidelines.
- There is no need for more frequent screening or to stop HRT prior to mammogram screening.

In women with a familial risk or high-risk benign breast condition, HRT exposure has not been shown to have an additive effect on the risk of diagnosis. These patients should be referred to a menopause specialist to discuss their management options.

Carriers of the BRCA1 and BRCA 2 gene mutation who have had risk-reducing bilateral salpingo-oopherectomy can be given HRT for symptom control and to reduce their risk of osteoporosis and cardiovascular disease, until the until the average age of menopause (51 years). A meta-analysis and recent systemic review on this showed no increase in the risk of breast cancer in women with BRCA mutations using HRT after BSO.[22,23]

*** Note: A history of breast cancer is a contraindication to systemic HRT - refer to a menopause specialist and oncologist / breast cancer team for advice.[33]**

Understanding the Risks of Breast Cancer[24]

Consilient Health

A comparison of lifestyle risk factors versus Hormone Replacement Therapy (HRT) treatment.

Difference in breast cancer incidence per 1,000 women aged 50-59.
Approximate number of women developing breast cancer over the next five years.

23 cases of breast cancer diagnosed in the UK general population

An additional four cases in women on combined hormone replacement therapy (HRT)

Four fewer cases in women on oestrogen only Hormone Replacement Therapy (HRT)

An additional four cases in women on combined hormonal contraceptives (the pill)

An additional five cases in women who drink 2 or more units of alcohol per day

An additional three cases in women who are current smokers

An additional 24 cases in women who are overweight or obese (BMI equal or greater than 30)

Seven fewer cases in women who take at least 2½ hours moderate exercise per week

Adapted from BMS Understanding Risks of Breast Cancer Tool.[24]

Troubleshooting: Minor Oestrogen Related Side Effects [36,37]

Minor Oestrogen related side effects

Breast tenderness/ Nipple sensitivity, Leg cramps, Nausea/ Indigestion, Bloating, Headaches, Irritability and Depression, Irregular bleeding or spotting (can occur during the first 4-6 months of starting HRT)

ACTION

Management Options:

1. Existing Patients: Reduce Oestrogen Dose. **New Patients:** If your patient is already sensitive to oestrogen, titrate up from a very low dose (25mcg patch, 1mg tablet, 1 spray or 1 pump of TD) until they can tolerate the hormone.

2. Delivering the oestrogen in pulses rather than sustained release- patches deliver oestrogen in a continuous feed over 3-4 days and this may have an impact on side effects and tolerance. If a patient is willing, change to a single daily application of oestrogen; the dose to be decided by the patient, until they adjust.

3. Change the delivery route (assuming an alternative delivery route is not contraindicated).

4. Prescribe a different Oestrogen Medicine

Note: It may take 3 to 4 months before tolerance is developed.

Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

Troubleshooting: Progestogen[7,8,9,25,36,37]

Consilient Health

PROGESTOGEN RELATED SIDE EFFECTS

Progestogen Side Effects

PMS-type symptoms, Irritability and Depression, Breast tenderness, Bloating, Headaches, Acne/greasy skin

Considerations:

1. Try a different Progestogen molecule- either as a single agent or with oestrogen in combination with HRT products.
See progestogen chapter for full details of progestogen.

2. Try minimising progestogen exposure - What is the minimum progestogen dose? The role of the progestogen part of HRT is to protect endometrium from the effects of the oestrogen and not as a therapeutic component for menopausal symptoms. There are studies to guide us as to how much progestogen would be required to ensure endometrial protection and they are:

Note: Progestogen doses outlined below are for women who are using ≤ 50mcg Oestrogen.

For non-menstruating patients, the minimum recommended Progestogen doses are:*

- 100mg Micronised progesterone daily
- 10mg Dydrogesterone daily
- 2.5mg Medroxyprogesterone acetate
- Mirena (for 5 years)

For menstruating patients, the minimum recommended Progestogen doses are:*

- 200mg Micronised progesterone x 12 days/month
- 10mg Dydrogesterone daily x 12 days per month is recommended
- 5mg Medroxyprogesterone acetate
- Mirena , Levonorgestrel available as a 52mg IUCD.

Long Cycle HRT

Long cycle progestogen regimes are sometimes recommended for patients with extreme progestogen sensitivity not improved by other options. This involves providing oestrogen all the time but only including a progestogen for 12 days every 3 months. Unfortunately patients will have side effects during these 12 days but they can schedule their progestogen days for a time that suits them better. The safety of 'Long Cycle Progestogen' HRT with regard to the lining of the womb is questionable and not routinely recommended. It is wise to offer ultrasound review of the endometrium for patients who can not use progestogen every month. Ideally this should be undertaken by a practitioner with specific menopause accreditation.

Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

*Other Progestogens / other doses of micronised progesterone are also available as Exempt Medicinal Products, information on the supply of these medicines can be provided from the manufacturer. Further information on Exempt Medicinal Products can also be found on the HPRA website, www.HPRA.ie

Troubleshooting: Testosterone Risk[16,17,18]

Consilient Health

Testosterone Related Side Effects

Testosterone in doses that approximate physiological testosterone concentrations for premenopausal women is associated with mild increases in acne and body or facial hair but not clitoromegaly/ change in voice or alopecia.

Oral testosterone therapy (but not transdermal therapy) is associated with adverse lipid profiles. It has not been associated with increases in blood pressure, blood glucose or HBA1C levels.

There is no association with changes in breast density on mammography and current data suggests that short-term transdermal therapy does not impact breast cancer risk. Testosterone should be used with caution in women who have a history of hormone-sensitive breast cancer.[18]

See further information in Testosterone chapter

Trouble shooting: Unscheduled Bleeding[5,26,27,28]

Note - bleeding that occurs in a postmenopausal women who is not on HRT, always requires investigation!

Bleeding soon after starting HRT is common and is often a cause of concern and inconvenience for patients.

An inadequate progestogenic effect can result in endometrial proliferation and possibly hyperplasia and bleeding.
The main goal is to exclude treatable causes of bleeding and to rule out malignancy.

Bleeding may result from medical interventions and medications, or as a result of bleeding dyscrasias, fibroids, endometrial polyps, hyperplasia or from cervical disease, genital infections or other local causes.

Bleeding that occurs while on Sequential / Cyclical HRT:

Withdrawal bleed is normal and this should be discussed with the patient.
It should occur toward the end of or after progestogen containing phase of the cyclical regimen.
Unpredictable/ unexpected bleeding is common in the first 6 months after starting HRT.
Bleeding which is unpredictable, occurring not at the expected time, or excessively heavy should be investigated.

Bleeding occuring while on Continuous HRT:

In women who are more than 12 months from their LMP, bleeding is common within the first 6 months of initiating HRT.

Investigation is not required within the first three months of initiating HRT and may respond to modification of HRT doses / delivery systems. Bleeding that does not respond to these fixes must be investigated. Risk factors for endometrial cancer include:

- Raised BMI
- History of polycystic ovarian syndrome (PCOS)
- Use of unopposed oestrogen or tamoxifen
- Nulliparity
- Increasing age (>45)
- Type 2 diabetes
- Family history (having close relatives with endometrial cancer)
- Having had endometrial hyperplasia in the past
- Treatment with radiation therapy to the pelvis to treat another cancer

Troubleshooting: Unscheduled Bleeding[5,26,27,28,36,37]

UNSCHEDULED BLEEDING PART 2

Bleeding that occurs beyond 6 months of use of HRT:

- Physical exam - exclude STI / cervical / local vulvovaginal causes of bleeding
- Discuss compliance
- Pelvic ultrasound;
- If on sequential HRT: aim to have ultrasound in the first week after bleeding starts
- Up to date cervical smear

Endometrial thickness > 5mm;

- Endometrial blind biopsy may miss focal pathology
- Refer to gynaecology for endometrial sampling/ hysteroscopy

Endometrial thickness < 5mm; Consider:

- Increasing to 21 days of progestogen (from 14) per cycle, if on sequential HRT
- Increasing the dose of progestogen for women taking continuous HRT
- Changing the progestogen to alternative stronger progestogen
- Decreasing oestrogen dose
- Mirena IUD

Tranexamic acid and mefanamic acid can be prescribed with HRT to reduce bleeding or dysmenorrhea

Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

Contraception During the Perimenopause[7,8,9,36,37 *]

Consilient Health

HRT use in patients on the following contraceptive methods:

1. The Combined Pill, Patch and Ring: Some patients will get relief from their menopause symptoms by hormonal contraception. If a combined hormonal contraception (CHC) is indicated for and acceptable to the patient, CHC is a suitable alternative to HRT- "No break / short break" regimes should be used so as to minimise gaps in the therapeutic effects of the hormone. Do not use CHC and HRT together.

2. The Progestogen Only Pill (Contraception): Current POP users can use an oestrogen and progestogen HRT regime in addition to POP. Progestogen in contraception is generally not high enough to guarantee endometrial protection so the additional progestogen in the HRT product is required.

3. Depo-Provera injection: It is thought that the Depo-provera injection will protect the endometrium from HRT oestrogen (but there is no data to support this). Advice is patients commencing are prescribed a HRT containing oestrogen and progestogen to convey endometrial protection.

4. Implanon: This may not provide enough endometrial protection. Additional progestogen as part of a HRT regime must be provided.

5. Mirena: For the first 5 years after insertion the LNG progestogen from the Mirena will suffice for the progestogen component of an HRT regime. After 5 years in situ, the Mirena will have to be changed or that Mirena can be left in situ and an additional progestogen as part of a HRT regime must be provided.

6. Kyleena, Jaydess, Copper IUCD, Barrier and Natural contraception: Provide contraceptive cover during the perimenopause, patients who require HRT should be prescribed both the oestrogen and the progestogen components of HRT.

All patients at risk of pregnancy should be counselled about contraception.
Advice given is based on the experience of practitioners working in this area. Please refer to the SPC for all medicines.

Special Considerations [7,8,9,29,30,33,34,35,36,37]

Migraine

Migraine, even migraine with aura, is not a contraindication to HRT use and may even be beneficial but some migraine sufferers may experience migraine flare up's. A cautious approach is recommended but there is no need to refer to a specialist. A non-oral route may provide a more stable delivery of the hormone and be preferable in migraine with aura sufferers.

Endometriosis

Oestrogen may aggravate dormant or settled endometrial deposits even after Hysterectomy +/- BSO so people with a past history of moderate to severe endometriosis should be considered for Oestrogen and Progestogen HRT as the addition of the progestogen may suppress any residual endometriotic tissue.

Premature Ovarian Insufficiency (POI)

POI is associated with significant increases in morbidity and mortality if not treated correctly. All patients should be assessed by an endocrinologist with a special interest in POI or a dedicated POI service. The need for oestrogen, progestogen and frequently testosterone replacement is often greater in this cohort and larger than standard doses of HRT are sometimes required. Even though POI is linked to subfertility, contraception is also required as there may be unpredictable ovarian follicular activity.

Epilepsy

Data to suggest that people with seizure disorder may experience a reduction in seizure control when initiating HRT / any oral sex hormone - advice is to start slow and low and TD. People using Rifampicin, phenytoin, barbiturates and phenylbutazone should avoid the progestogen NET as its metabolism is accelerated by these medications which will weaken the endometrial protection they provide. This applies to users of Noriday (3 daily) or the Evorel conti patch.[37]

Advice given is based on the experience of practitioners working in this area. Advice for Evorel Conti is as per SPC. Please refer to the relevant SPC for all other medicines.

Special Considerations [7,8,9,29,30,33,34,35,36,37]

Osteoporosis

50% of women & 20% of men will experience an osteoporosis-related fracture in their lifetime.[29]

- HRT is both a treatment and a prevention therapy for osteoporosis. Standard dose of MHT reduces the risk of femoral, vertebral and non-vertebral fractures.
- On cessation of HRT bone protection is rapidly lost.
- An alternative regime should be prescribed before stopping HRT.
- It is believed, but not proven, that the efficacy of HRT in reducing fracture risk is derived from low dose (25mcg) oestrogen[30].
- Postmenopausal women need a dietary reference intake (DRI) of 800 - 1000 iu of vitamin D and 1,000 mg to 1,500mg of elemental calcium in the postmenopausal period. This should be assessed for each individual, a calcium dietary calculator can be used such as the Osteoporosis Foundation Calcium Calculator on the www.osteoporosis.foundation website.[33,34,35].

Specialist menopausal medical advice and management is advised for the following cohort of symptomatic women:

- Women whose treatment within primary care settings does not improve their menopausal symptoms.
- Women who are experiencing on-going troublesome or clinically significant side effects further to treatment within primary care setting, e.g. bleeding.
- Women who have contraindicaitons to HRT.
- Women with a complex medical history.[33]

Advice given is based on the experience of practitioners working in this area. Please refer to the relevant SPC for all medicines.

Prescribing Information: Evorel 50® and Evorel Conti® [36,37]

Consilient Health

Abbreviated Prescribing Information EVOREL® 50 (estradiol/patch) & EVOREL® Conti (estradiol hemihydrate norethisterone acetate)
Please Please consult the Summary of Characteristics for all contraindications, adverse reactions, and full prescribing information

Healthcare professionals should report any suspected adverse events to HPRA Pharmacovigilance, Earlsfort Terrace, Dublin 2 **Tel: 01 6764971,** or at **www.hpra.ie**, **email: medsafety@hpra.ie.**
Suspected adverse events should also be reported to Consilient Health Ltd.,
Tel: 01 2057766 or **drugsafety@consilienthealth.com**

Presentation: Evorel 50: 3.2mg estradiol patch; Evorel® Conti 3.2 mg of estradiol hemihydrate and 11.2 mg of norethisterone acetate transdermal patch. **Indication:** HRT for oestrogen deficiency symptoms in post-menopausal women. Evorel 50, Prevention of osteoporosis in post-menopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. Evorel® Conti only in postmenopausal women more than 6 months post-menopause. **Dosage & administration:** Evorel® is an oestrogen-only HRT and Evorel® Conti is a continuous combined HRT preparation. The administration is identical for both products, which should be applied to the skin twice weekly. For initiation and continuation of treatment of menopausal symptoms, the lowest effective dose for the shortest duration should be used. For women with an intact uterus progestogen should normally be added to Evorel® for the prevention of adverse endometrial effects, e.g. hyperplasia and cancer. The regimen may be either cyclic or continuous sequential. Only progestogens approved for addition to oestrogen treatment may be prescribed. Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women. ***Treatment of oestrogen deficiency symptoms & Prevention of post-menopausal osteoporosis:*** Therapy should be started with one Evorel® 50 patch (delivering 50 µg of estradiol/24 hours). Evorel® Conti is a single dose patch. ***Guidance on how to start therapy and Switching from other HRT:*** See full prescribing information. **Method of Administration:** Evorel® and Evorel® Conti should be applied to the skin as soon as it is removed from the wrapper. Recommended application sites are on clean, dry, healthy, intact skin and each application should be made to a slightly different area of skin on the trunk below waistline. Should not be applied on or near the breasts. Only one patch should be applied at a time. ***Children:*** Not indicated in children. ***Elderly:*** Not indicated in children. Elderly: Data are insufficient in the elderly (>65 years old). ***Route of administration:*** Transdermal use. **Contraindications:** Known, current or past or suspected breast cancer. Known or suspected oestrogen-dependent malignant tumours (e.g., endometrial carcinoma). Undiagnosed genital bleeding. Untreated endometrial hyperplasia. Previous or current VTE, thrombophlebitis. Active or recent past ATE disease. Acute liver disease, or a history of liver disease if liver function tests have failed to return to normal. Known thrombophilic conditions. Known hypersensitivity to the active substances or to any of the excipients. Porphyria.
Special warnings and precautions for use: Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. ***Conditions which need supervision: For the full list see the relevant SmPC. Conditions which require monitoring while on oestrogen therapy:*** Oestrogens may cause fluid retention. Cardiac or renal dysfunction should be carefully observed. Disturbances or mild impairment of liver function. A full list is found in the relevant SmPC. ***Therapy should be discontinued if a contraindication is discovered and in the following situations:*** jaundice/ deterioration in liver function, significant increase in blood pressure, new onset of migraine-type headache, pregnancy. **Interactions:** The metabolism of oestrogens (and progestogens) may be increased by concomitant use of substances known to induce drugmetabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants, anti-infectives and bosentan. Ritonavir, nelfinavir and herbal preparations containing St. John's Wort may induce the metabolism of oestrogens and progestogens. Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile. Caution is warranted with HCV drug combinations as ALT elevations have been seen in clinical trials. See relevant SmPC for full details. Hormone contraceptives containing oestrogen have been shown to significantly decrease plasma concentrations of lamotrigine when co- administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Therefore, dose adjustment of lamotrigine may be necessary. **Pregnancy and lactation:** Not indicated, treatment should be withdrawn immediately. **Side effects: Very common:** Application site pruritus, Application site rash. **Common:** Depressed mood, Migraine, Dizziness, Headache, Abdominal pain, Diarrhoea, Nausea, Pruritus, Rash, Arthralgia, Breast pain, Metrorrhagia, Pain, Application site erythema, Application site oedema, Weight increased and Hypersensitivity (Evorel® Conti only). **Uncommon include** Genital candidiasis, Palpitations, Myalgia, Dysmenorrhoea, Oedema, Oedema peripheral. **Rare:** Breast cancer, Epilepsy, Thrombosis, Abdominal distension, Cholelithiasis, **Frequency not known:** Endometrial cancer, Cerebrovascular accident, Myocardial infarction, Deep vein thrombosis, Pulmonary embolism, Angioedema. **Package Quantities & Cost:** Evorel® 50 GMS Price: 8 €5.21 Evorel® Conti GMS Price: 8 €13.54. **Marketing authorisation number:** Evorel 50 PA22668/008/001,VEvorel Conti PA22668/009/001. **Marketing authorisation holder:** Theramex Ireland Limited, 3rd Floor, Kilmore House, Park Lane, Spencer Dock, Dublin 1, D01 YE64, Ireland **Legal classification:** POM. **Date of Preparation of API:** November 2024.

IE-EVC-100(5). Date of Preparation: November 2024.

PRESCRIBING INFORMATION

Prescribing Information: Blissel® Vaginal Gel[42]

PRESCRIBING INFORMATION: Please refer to Summary of Product Characteristics (SmPC) before prescribing.
ACTIVE INGREDIENT: 1g vaginal gel contains 50 micrograms estriol.
INDICATIONS: Treatment of symptoms of vaginal atrophy due to estrogen deficiency in postmenopausal women.
DOSAGE AND ADMINISTRATION: Use the lowest effective dose for the shortest duration. **Treatment initiation or reinstitution:** One applicator-dose per day for 3 weeks at bedtime. Only initiate local estrogen therapy for symptoms that adversely affect quality of life. Take a complete personal and family medical history. Use this, and the contraindications and warnings for use, to guide physical (including pelvic and breast) examination. Treat vaginal infections before starting therapy. **Maintenance treatment:** One applicator-dose twice weekly emptied into vagina at bedtime. **Evaluation:** Evaluate treatment continuation after 12 weeks. Conduct periodic check-ups and investigations, adapted to the individual, including mammography, in accordance with accepted screening practices. Advise of breast changes that should be reported.
Appraise the risks and benefits at least annually and continue only if the benefit outweighs the risk. Administer a missed dose as soon as remembered. Skip doses 12 hours or more overdue and administer the next dose at the normal time. **Administration:** Empty dose-marked applicator into vagina in accordance with instructions in the information leaflet.
CONTRAINDICATIONS: Known, past or suspected breast cancer, known or suspected estrogen-dependent malignant tumour, undiagnosed genital bleeding, untreated endometrial hyperplasia, previous idiopathic or current venous thromboembolism, active or recent arterial thromboembolic disease, known thrombophilic disorders, acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal, porphyria, hypersensitivity to the active substance or to any of the excipients. Discontinue immediately if a contraindication is discovered and in cases of jaundice or deterioration in liver function, significant increase in blood pressure, new onset of migraine-type headache or pregnancy.
SPECIAL WARNINGS AND PRECAUTIONS: Do not combine with estrogen preparations for systemic treatment. Intravaginal applicator may cause minor local trauma, especially in women with serious vaginal atrophy. Excipients may cause allergic reactions (possibly delayed). Close supervision of patients with current, previous, or where the condition has been aggravated during pregnancy, or previous hormone treatment: Leiomyoma or endometriosis, risk factors for thromboembolic disorders or estrogen-dependent tumours, hypertension, liver disorders, diabetes mellitus with or without vascular involvement, cholelithiasis, migraine or (severe) headache, systemic lupus erythematosus, history of endometrial hyperplasia, epilepsy, asthma, otosclerosis. Addition of a progestogen is not recommended. Endometrial safety of long-term (> one year), or repeated use of, vaginal oestrogen is uncertain so treatment should be reviewed at least annually.
Investigate breakthrough bleeding or spotting occurring at any time on therapy to exclude endometrial malignancy. Caution in women who have undergone hysterectomy because of endometriosis, especially if there is residual endometriosis. Risks associated with systemic HRT apply to a lesser extent for vaginally applied oestrogens but they should be considered in case of long term or repeated use. Epidemiological evidence from a large meta-analysis suggests no increase in risk of breast cancer in women with no history of breast cancer taking low dose vaginally applied oestrogens. It is unknown if low dose vaginal oestrogens stimulate recurrence of breast cancer. Increased risk of ovarian cancer, venous thromboembolism (VTE), coronary artery disease and ischaemic stroke associated with systemic HRT.
Generally recognised risk factors for VTE include use of estrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m2), pregnancy/ postpartum period, systemic lupus erythematosus and cancer. No consensus about the possible role of varicose veins in VTE. Estrogens with systemic effects may cause fluid retention or increase of plasma triglycerides. Therefore, careful observation of patients with heart diseases or impaired renal function or with pre-existing hypertriglyceridemia during the first weeks of treatment is recommended. No systemic effects expected with Blissel low dose estriol vaginal gel. Careful observation in severe renal insufficiency as levels of circulating estriol may be increased.
INTERACTIONS: No interaction studies have been performed. Due to vaginal administration, and minimal systemic absorption, no clinically relevant interactions are expected. Consider interactions with other locally applied vaginal treatments.
FERTILITY, PREGNANCY, LACTATION: No fertility data available. Not indicated during pregnancy. Withdraw treatment immediately if pregnancy occurs. No data available on exposed pregnancies. No indicated during lactation.
DRIVING: No influence on ability to drive and use machines.
UNDESIRABLE EFFECTS: Very common: None. **Common:** Pruritus genital, application site pruritus, pruritus. Consult SmPC in relation to less common side effects and class effects associated with systemic HRT.
PHARMACEUTICAL PRECAUTIONS: Store below 25°C.
LEGAL CATEGORY: POM.

Product	Blissel®
Net Wholesale Price	€16.50
Pack Size	30g
Marketing Authorisation Number	PA2102/001/001

MARKETING AUTHORISATION HOLDER: Italfarmaco S.A., San Rafael 3, 28108 Alcobendas (Madrid), Spain. Marketed and distributed in Ireland by Consilient Health (Ireland) Ltd, Block 2A Richview Office Park, Clonskeagh, Dublin 14, D14 Y045. E-mail: irishoffice@consilienthealth.com.

Adverse events should be reported. Reporting forms and information can be found at **http://www.hpra.ie/homepage/medicines/safety-information/reportingsuspected-side-effects**. Adverse events should also be reported to Consilient Health (Ireland) Ltd, Block 2A Richview Office Park, Clonskeagh, Dublin 14, D14 Y045 or **drugsafety@consilienthealth.com**

Information about this product, including adverse reactions, precautions, contraindications, and method of use can be found at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2102-001-001_09082022145537.pdf IE-BLS-158(3)) Date of Preparation October 2024

PRESCRIBING INFORMATION

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Consilient Health

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For further information and support visit www.Consilienthealth.ie and www.Evorel.ie [36,37]

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