Medicines Management Programme

Medicinal products for hormone replacement therapy (HRT)

Prescribing guidance in response to product shortages

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Abbreviations

BMS	British Menopause Society
CDS	Community Drug Schemes
DP	Drugs Payment (scheme)
EMP	Exempt medicinal product
GMS	General Medical Services
HPRA	Health Products Regulatory Authority
IUS	Intrauterine system
HRT	Hormone replacement therapy
HSE	Health Service Executive
IMS	International Menopause Society
LNG-IUS	Levonorgestrel-intrauterine system
MMP	Medicines Management Programme
NICE	National Institute for Health and Care Excellence
NMIC	National Medicines Information Centre
PCRS	Primary Care Reimbursement Service
POI	Premature ovarian insufficiency
RCOG	Royal College of Obstetricians and Gynaecologists
SmPC	Summary of Product Characteristics
VTE	Venous thromboembolism

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Definitions

For the purposes of this document, the reimbursement price refers to the price as listed on the reimbursement list, available on the Health Service Executive (HSE)-Primary Care Reimbursement Service (PCRS) website (www.pcrs.ie). Reimbursement prices are correct as of 1st September 2022, unless otherwise stated.

An exempt medicinal product (EMP) is a medicinal product that is not authorised in Ireland either by the Health Products Regulatory Authority (HPRA) or in the case of a centrally authorised medicinal product, by the European Commission (via the European Medicines Agency), but which can be legally supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of a registered medical practitioner or registered dentist for use by their individual patients on her/his direct personal responsibility, in order to fulfil the special needs of those patients.[1]

Off-label use refers to the use of an authorised medicinal product outside the terms of its marketing authorisation or product registration.

Hormone replacement therapy (HRT) for the treatment of menopause is also known as menopausal hormone therapy or postmenopausal hormone therapy.

'Sequential HRT' may also be referred to as 'cyclical HRT' and these terms may be used interchangeably.

1. Purpose

The purpose of this document is to outline the different formulations and preparations of hormone replacement therapy (HRT) currently authorised in Ireland and to offer suggestions for alternatives where supply issues may exist, as part of the Health Service Executive (HSE)-Medicines Management Programme's (MMP) remit to support safe, effective and cost-effective prescribing in the Irish healthcare setting.

This document was initially developed in 2020 in response to transdermal HRT patch supply issues but was updated in 2022, to reflect the persistent product shortages across this therapeutic area.

2. Scope

This document considers HRT medicinal products authorised and currently marketed in Ireland for the management of menopausal symptoms. Where a supply issue has been identified, this document will consider alternatives where appropriate.

3. Menopause

Menopause is the process when menstrual cycles stop.[2] It is caused by ovarian failure and is recognised as having occurred after 12 consecutive months of amenorrhoea. Ovarian failure results in changing hormone levels, giving rise to oestrogen deficiency.[3-5] Menopause occurs at an average age of 51-52 years (range from 45-55 years).[5,6]

Menopause is a gradual process during which individuals experience perimenopause before reaching postmenopause.[2,3] Perimenopause (also known as the menopausal transition) is defined as the time during which the individual experiences symptoms and cycle variability until 12 months after the final menstrual period.[3] Postmenopause refers to the time after menopause has occurred, starting when an individual has not had a menstrual period for 12 months.[3]

Symptoms occurring during the menopausal process include irregular bleeding (perimenopause), vasomotor symptoms (e.g. hot flushes and night sweats) and vulvovaginal atrophy.[3,5]

Menopause transition can have a significant impact on those affected, with more than 75% experiencing vasomotor symptoms and 25% describing their symptoms as severe.[7,8] A third experience long-term symptoms,[8] which may last a median duration of seven years and persisting for up to 15 years in 20% of women.[7]

4. Hormone replacement therapy (HRT)

HRT remains the most effective therapy for relieving vasomotor symptoms and vulvovaginal atrophy[5] and is associated with significant improvement in overall quality of life.[8] Individuals with vasomotor symptoms require systemic HRT while those who experience vulvovaginal atrophy may only require local oestrogen.[7]

Individuals with an intact uterus require a combination of oestrogen and progestogen (combined HRT) to reduce the risk of endometrial hyperplasia and endometrial cancer associated with unopposed oestrogen exposure, while those who have had a hysterectomy only require oestrogen.[3,5,6,9]

Combined HRT can be further sub-divided into sequential (or cyclical) HRT and continuous combined HRT (see Section 7.3 below for further detail). Table 1 summarises HRT regimens for systemic use. Currently marketed HRT medicinal products will be described in more detail in Section 7 (illustrated in Appendix A- *Prescribing Tips and Tools in response to HRT product shortages*).

Table 1: Systemic hormone replacement therapy regimens[6,10]

Perimenopausal	Postmenopausal
Intact uterus	**Intact uterus**
• Combination of oestrogen and progestogen ➢ Sequential regimen ➢ Oestrogen and 52 mg LNG-IUS*	• Combination of oestrogen and progestogen ➢ Sequential regimen ➢ Continuous combined regimen ➢ Oestrogen and 52 mg LNG-IUS* • Tibolone
Hysterectomy	**Hysterectomy**
• Oestrogen alone	• Oestrogen alone • Tibolone

*LNG-IUS: levonorgestrel-intrauterine system (Mirena® IUS)

5. Availability of HRT

Shortages of HRT medicinal products were reported in a number of countries in 2019 and 2020, including Ireland. These shortages have continued to persist in subsequent years, inclusive of 2022.[11]

The Health Products Regulatory Authority (HPRA) monitors and reports on such medicine shortages and updates information as it becomes available. Suppliers have, in previous years, stated that shortages relate to both the active substance availability and manufacturing delays.[11] More recent

shortages have also been attributed to the significant increase in demand for HRT medicinal products over the last number of years.[12]

While manufacturers have increased production of HRT medicinal products in response to the increasing demand, issues remain in terms of availability to supply the market. These shortages have a tendency to result in periods of intermittent supply in some cases, but also periods of more prolonged product shortages.[12]

During supply disruptions, alternative treatments are generally available to meet individual needs, however there may be a requirement to use an alternative route of administration or to use two HRT medicinal products rather than one (i.e. oestrogen and progestogen as two separate products rather than one combination product). Switching an individual between products (due to supply issues) must involve a discussion with the individual, a review of symptoms, and shared decision making based on the risk-benefit profile and other patient factors.

In order for medicines to be reimbursed under the Community Drug Schemes (CDS) i.e. General Medical Services (GMS) and Drugs Payment (DP) schemes, they must have a reimbursement code. Some HRT medicinal products are marketed in Ireland, but their marketing authorisation holder has not applied for reimbursement under the CDS and therefore these treatments are only available for individuals to purchase privately on prescription. This should also be considered when choosing a HRT medicinal product or regimen for an individual.

Tables 2-6 below list HRT medicinal products along with their reimbursement codes where applicable and the HSE-Primary Care Reimbursement Service (PCRS) reimbursement price (available on www.pcrs.ie). The prices listed do not include VAT where applicable, mark-up or dispensing fees that private/DP scheme patients may be charged.

6. Formulations of HRT

Oestrogen alone, progestogen and combined HRT are available in a variety of preparations with different routes of administration and different associated risk factors.[13,14]

Different formulations for individual types of HRT that are marketed in Ireland as of September 2022 are outlined in Section 7 (illustrated in Appendix A- *Prescribing Tips and Tools in response to HRT product shortages*).

- **Oral tablets**

  A wide range of HRT oral tablets are available. They may contain oestrogen alone, progestogen or a combination of oestrogen and progestogen (combined HRT) as either continuous or sequential HRT.[13,14]

- **Transdermal formulations**

  HRT transdermal formulations are available as a transdermal patch, gel or spray.[13,14] There is a lower risk of venous thromboembolism (VTE) associated with the transdermal route of estradiol compared to the oral route.[3,6-8,15]

  - **Transdermal patches**

    Transdermal patches may contain oestrogen alone or a combination of oestrogen and progestogen (combined HRT). The patches are applied to any area below the waist[16,17] or abdomen[16-21] and should not be applied to the breasts.[16-21]

  - **Transdermal gel**

    Oestrogen alone is also available as systemic therapy in the form of a transdermal gel. It is applied once a day to a clean, dry, unbroken area of skin, usually on the lower trunk or right or left thigh[22] or upper arm, shoulder or inner thigh.[23] It should not be applied on or near the breasts.[22,23]

  - **Transdermal spray**

    Oestrogen alone is also available as a systemic therapy in the form of a transdermal spray. One metered-dose spray should be administered once daily to the dry and healthy skin of the forearm as a starting dose. The dose may be increased to two metered-dose sprays daily to the forearm based on clinical response.[24]

Local (vaginal) formulations

Vaginal oestrogen (local HRT) preparations including vaginal creams, vaginal tablets or vaginal pessaries contain a small amount of oestrogen. They are indicated for symptoms of vaginal atrophy related to oestrogen deficiency in postmenopausal women.[9] Local HRT will not improve other symptoms, such as hot flushes, or protect against the longer term effects of menopause such as osteoporosis. The risks that are associated with systemic HRT have not been identified with local low-dose oestrogen therapy.[4,8]

Practice point

- **Use of oral HRT has been associated with a significantly increased risk of VTE compared to no exposure.**
- **Transdermal HRT is associated with a lower risk of VTE than oral HRT formulations.**

✓ **The TRANSDERMAL ROUTE OF ADMINISTRATION (e.g. patch, gel or spray) should be considered as the preferred route for oestrogen in individuals with risk factors for venous thrombosis or stroke.**

7. HRT medicinal products authorised in Ireland

The following sections summarise the currently authorised HRT medicinal products (or EMP alternatives where appropriate) in Ireland.

7.1 Oestrogen (alone) HRT

Oestrogen alone HRT is suitable for individuals who have had a hysterectomy (or it must be used in combination with a progestogen medicinal product for individuals with an intact uterus).[3,4,7]

Oestrogen alone HRT is available in a number of different formulations:

- oral tablet
- transdermal patch
- transdermal gel
- transdermal spray
- local (vaginal) formulation.[14]

Table 2 outlines systemic oestrogen alone containing medicinal products authorised in Ireland and associated formulations and reimbursement price.[13,14]

Table 2: Systemic oestrogen alone medicinal products authorised in Ireland[13,16,18-29]

Product	Formulation	Ingredient(s)	Strength	Pack Size	Reimbursement	
					code	price
Oestrogen alone transdermal formulations						
Estradot® transdermal	transdermal patch	estradiol (as hemihydrate)	37.5 mcg per 24 hours	8	68314	€6.03
Evorel® 50	transdermal patch	estradiol (as hemihydrate)	50 mcg per 24 hours	8	24425	€5.21
Estradot® transdermal	transdermal patch	estradiol (as hemihydrate)	50 mcg per 24 hours	8	57226	€6.47
Estradot® transdermal	transdermal patch	estradiol (as hemihydrate)	75 mcg per 24 hours	8	48323	€7.60
Estradot® transdermal	transdermal patch	estradiol (as hemihydrate)	100 mcg per 24 hours	8	47415	€7.65
Oestrogel® actuation gel	transdermal gel	estradiol (as hemihydrate)	750 mcg per pump actuation (0.06% w/w)	80 g (64-doses)	24550	€5.80
Divigel® 0.1 %	transdermal gel	estradiol (as hemihydrate)	1 mg per sachet (0.1% w/w)	28	21272	€9.33
Lenzetto® transdermal	transdermal spray	estradiol (as hemihydrate)	1.53 mg per spray	6.5 ml (56 sprays)	78085	€8.52
Oestrogen alone oral tablet						
Fematab®	oral tablet	estradiol (as hemihydrate)	1 mg	28	24547	€1.38
Fematab®	oral tablet	estradiol (as hemihydrate)	2 mg	28	24536	€2.80
Estrofem®	oral tablet	estradiol (as hemihydrate)	2 mg	28	23655	€4.52
Premarin®	oral tablet	conjugated oestrogens	0.625 mg	28	62063	€2.69
Premarin®	oral tablet	conjugated oestrogens	1.25 mg	28	62071	€3.18

Abbreviations: mg: milligram; mcg: microgram. **Note:** all products with a reimbursement code are available under the DP scheme (maximum of €80 per month)/GMS (€1.50/€1.00 per item) (correct as of September 2022). Refer to individual SmPCs (www.hpra.ie) for further details.

7.2 Progestogen

Progestogens (see Table 3) are indicated as an adjunct to oestrogens for people with an intact uterus.[3,5,6,9] A variety of progestogens in differing strengths are available in progestogen alone preparations and as combination products.[13,14]

Table 3 outlines progestogen alone medicinal products available in Ireland and associated formulations and reimbursement price.

Table 3: Progestogen alone medicinal products available in Ireland[13,30-36]

Product	Formulation	Ingredient(s)	Strength	Pack Size	Reimbursement	
					code	price
Progestogen oral formulations						
Duphaston®	oral tablet	dydrogesterone	10 mg	42	22818	€8.81
Provera®	oral tablet	medroxyprogesterone acetate	10 mg	90	43645	€19.32
Provera®*	oral tablet	medroxyprogesterone acetate	5 mg	30	Not reimbursed	
Utrogestan®*	oral capsule (EMP)	micronised progesterone	100 mg	30	20237	Refer to PCRS circular 40/16 (www.pcrs.ie)
Utrogestan®**	oral capsule (EMP)	micronised progesterone	200 mg	15	20238	
Progestogen intrauterine system						
Mirena® IUS	LNG-IUS	levonorgestrel	52 mg	1	33578	€116.50 (5 yrs)

Abbreviations: EMP: Exempt medicinal product; IUS: intrauterine system; mg: milligram; LNG-IUS: levonorgestrel-intrauterine system; PCRS: Primary Care Reimbursement Service. **Note:** all products with a reimbursement code are available under the DP scheme (maximum of €80 per month)/GMS (€1.50/€1.00 per item) (correct as of September 2022). Refer to individual SmPCs (www.hpra.ie) for further details.

*Authorised product is not marketed in Ireland but an EMP alternative is available.
**Not authorised in Ireland but available as an EMP.

Combination products outlined in Section 7.3 allow for administration of both oestrogen and progestogen in one product (oral tablets or transdermal patches). However, if supply issues occur with combination products, prescribing products separately as oestrogen transdermal formulations and oral or intrauterine progestogen products could be considered. See Tables 2 and 3.

Further information on individual progestogen alone medicinal products

- Dydrogesterone is indicated in association with oestrogen in HRT. The standard oral dose of dydrogesterone is 10 mg daily for the last 14 days of each 28 day oestrogen treatment cycle, in women on sequential (cyclical) HRT.[30]

    - Professional organisations, such as the British Menopause Society (BMS), suggest that dydrogesterone, with transdermal estradiol, should be considered, in women who are at increased risk of stroke.[7]

- Oral medroxyprogesterone acetate is indicated for adjunctive use with oestrogen in HRT in post-menopausal women at a dose of 10 mg daily for 10 to 12 days, beginning on day 16 of a 28-day course of oestrogen therapy, in women on sequential (cyclical) HRT.[32]

- Off-label continuous use of oral medroxyprogesterone acetate 5 mg tablets can be used as the progestogen component of continuous combined HRT and is recommended by professional organisations such as the BMS.[37]
- Medroxyprogesterone acetate 5 mg tablets are currently authorised in Ireland but are not marketed by the company, however an EMP alternative is available.[31]

- Progestogen, as a levonorgestrel-intrauterine system (LNG-IUS) 52 mg (Mirena® IUS), is indicated for protection from endometrial hyperplasia during oestrogen replacement therapy.[35] Mirena® IUS is recommended by professional organisations such as the BMS.[37]

- Micronised progesterone oral capsules are indicated for adjunctive use with oestrogen in postmenopausal women with an intact uterus, as HRT.[33,34] Micronised progesterone has been found to have a more selective effect on progesterone receptors and it results in less interaction with androgenic and mineralocorticoid receptors compared with other progestogens.[7] Evidence suggests that oral micronised progesterone effectively protects the endometrium from the stimulatory effects of oestrogen and has a reduced risk of breast cancer compared to other progestogens.[38-40] Professional organisations, such as the BMS, suggest that micronised progesterone, with transdermal estradiol, should be considered, in women requiring HRT, who are at increased risk of stroke.[7]

  - Micronised progesterone (Utrogestan®) 100 mg oral capsules are currently authorised in Ireland but are not marketed by the company, however an EMP alternative is available.[33] Micronised progesterone (Utrogestan®) 200 mg oral capsules are currently not authorised in Ireland but are available as an EMP.[34]
  - The oral dose of micronised progesterone for sequential HRT therapy is 200 mg daily for 12 days from day 15 to day 26 or 100 mg daily from day 1 to day 25 (withdrawal bleeding being less with the latter treatment schedule).[33,34]
  - Off-label use of oral micronised progesterone 100 mg daily at night is often used as the progestogen component of continuous combined HRT and is recommended by professional organisations including the International Menopause Society (IMS) and the BMS.[4,37]

- The BMS also suggests that 1.05 mg of norethisterone (off-label use) would provide sufficient progestogen cover when taken orally on a continuous basis.[37]

Practice point

When using oral progesterone to compliment transdermal oestrogen delivery, ensure that the individual is fully aware of the importance of COMPLIANCE with the progestogen component for safety and to reduce cancer risks.

7.3 Combined HRT

Combined HRT (oestrogen and progestogen) is necessary for individuals with an intact uterus who require HRT, either as sequential (cyclical) HRT or continuous combined HRT.[3,4] Continuous combined HRT is indicated for people in postmenopause, where it has been more than 12 months since their last menstrual period.[9]

7.3.1 Sequential HRT

Sequential (cyclical) HRT consists of continuous administration of oestrogen and cyclical administration of progestogen (for 10 to 14 days). Sequential HRT is indicated for people in perimenopause or in the early postmenopause.[41] Women taking sequential HRT have a monthly withdrawal bleed which is often light.[41] Sequential HRT medicinal products are authorised only as oral tablets in Ireland (Table 4). Table 4 outlines sequential HRT medicinal products authorised in Ireland and associated formulations and reimbursement price.[13,14]

Table 4: Sequential (cyclical) hormone replacement therapy medicinal products authorised in Ireland[13,42-45]

Product	Formulation	Ingredient(s)	Strength	Pack Size	Reimbursement	
					code	price
Sequential (cyclical) HRT oral tablet						
Novofem®	oral tablet	estradiol (as hemihydrate)/ norethisterone acetate	• 1 mg estradiol (16 days) • 1 mg estradiol/1 mg norethisterone acetate (12 days)	84	15628	€14.77
Trisequens®	oral tablet	estradiol (as hemihydrate)/ norethisterone acetate	• 2 mg estradiol (12 days) • 2 mg estradiol/1 mg norethisterone acetate (10 days) • 1 mg estradiol (6 days)	28	48844	€4.96
Femoston®	oral tablet	estradiol (as hemihydrate)/ dydrogesterone	• 1 mg estradiol (14 days) • 1 mg estradiol/10 mg dydrogesterone (14 days)	28	34236	€5.82
Femoston®	oral tablet	estradiol (as hemihydrate)/ dydrogesterone	• 2 mg estradiol (14 days) • 2 mg estradiol/10 mg dydrogesterone (14 days)	28	24143	€5.82

Abbreviations: HRT: Hormone replacement therapy; mg: milligram. **Note:** all products with a reimbursement code are available under the DP scheme (maximum of €80 per month)/GMS (€1.50/€1.00 per item) (correct as of September 2022). Refer to individual SmPCs (www.hpra.ie) for further detail.

To achieve sequential HRT with other formulations, individuals could use an oestrogen transdermal formulation with an oral progestogen. Examples of oral progestogens which can be used in this setting are dydrogesterone, medroxyprogesterone acetate, or micronised progesterone. Refer to Section 7.2 and the SmPC for individual dosages.[30,32,34,37]

See Tables 2 and 3 for available medicinal products.

7.3.2 Continuous combined HRT

Continuous combined HRT is an option for people in postmenopause from 12 months after their last menstrual period.[9] It consists of daily combined oestrogen and progestogen, (one tablet a day or regular release from a transdermal patch) for 28 days.

The majority of people have no bleeding on continuous combined HRT after 12 months.[6] Table 5 outlines continuous combined HRT medicinal products authorised in Ireland and associated formulations and reimbursement price.[13,14]

Table 5: Continuous combined hormone replacement therapy medicinal products authorised in Ireland[13,17,46-53]

Product	Formulation	Ingredient(s)	Strength	Pack Size	Reimbursement	
					code(s)	price
Continuous combined HRT transdermal formulations						
Evorel Conti®	transdermal patch	estradiol (as hemihydrate)/ norethisterone acetate	50 mcg estradiol/170 mcg norethisterone acetate per 24 hours	8	24560	€13.54
Continuous combined HRT oral tablet						
Kliogest®	oral tablet	estradiol (as hemihydrate)/ norethisterone acetate	2 mg estradiol/1 mg norethisterone acetate	28	31283	€6.21
Activelle®	oral tablet	estradiol (as hemihydrate)/ norethisterone acetate	1 mg estradiol /0.5 mg norethisterone acetate	28	10454	€7.57
Angeliq®	oral tablet	estradiol (as hemihydrate) /drospirenone	1 mg estradiol /2 mg drospirenone	84	12463	€39.15
Indivina®	oral tablet	estradiol valerate/ medroxyprogesterone acetate	1 mg estradiol valerate/2.5 mg medroxyprogesterone acetate	28 84	29020 29032	€8.31 €24.92
Indivina®	oral tablet	estradiol valerate/ medroxyprogesterone acetate	1 mg estradiol valerate/5 mg medroxyprogesterone acetate	84	29054	€24.92
Indivina®	oral tablet	estradiol valerate/ medroxyprogesterone acetate	2 mg estradiol valerate/5 mg medroxyprogesterone acetate	84	29096	€24.92
Femoston Conti®	oral tablet	estradiol (as hemihydrate)/ dydrogesterone	0.5 mg estradiol/ 2.5 mg dydrogesterone	84	36925	€24.40
Femoston Conti®	oral tablet	estradiol (as hemihydrate)/ dydrogesterone	1 mg estradiol/ 5 mg dydrogesterone	28	24164	€7.86

Abbreviations: HRT: Hormone replacement therapy; mg: milligram; mcg: microgram. **Note:** all products with a reimbursement code are available under the DP scheme (maximum of €80 per month)/GMS (€1.50/€1.00 per item) (correct as of September 2022). Refer to individual SmPCs (www.hpra.ie) for further detail.

To achieve continuous combined HRT with alternative formulations individuals could use oestrogen alone as an oestrogen transdermal formulation (Table 2) **and** LNG-IUS 52 mg (Mirena® IUS) or oral progestogen daily (Table 3). Oral progestogens are not authorised for continuous use in this way however off-label daily use of oral progestogens is recommended by some professional organisations including the IMS and the BMS.[4,37] The recommended dosages of oral progestogens in this setting are micronised progesterone (Utrogestan®) 100 mg[i] oral capsule at night daily on a continuous basis or,[33,37] or medroxyprogesterone acetate (Provera®) 5 mg[i] orally daily on a continuous basis.[31,37] Note that Provera® 5 mg is not reimbursed under the CDS.[13]

See Tables 2 and 3 for available medicinal products.

7.4 Tibolone

Tibolone is a synthetic steroid that has oestrogenic, progestogenic and weak androgenic activity; it is less effective than oestrogen therapy in reducing vasomotor symptoms.[41] Tibolone is associated with an increased risk of breast cancer, stroke and endometrial cancer.[54]

Tibolone is indicated for the treatment of oestrogen deficiency symptoms in postmenopausal women, more than one year after menopause or as second line therapy for prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.[54]

It is a synthetic form of 'period-free' HRT, and is therefore another option for those in the postmenopausal phase, with either an intact uterus or hysterectomy.[54]

7.5 Local (vaginal) oestrogen

Table 6 outlines local HRT medicinal products (oestrogen containing) authorised in Ireland and associated formulations and reimbursement price.[13,14]

[i] Authorised product is not marketed in Ireland but an EMP alternative is available.

Table 6: Local hormone replacement therapy medicinal products authorised in Ireland[13,55-58]

Product	Formulation	Ingredient(s)	Strength	Pack Size	Reimbursement	
					code(s)	price
Local oestrogen (vaginal) medicinal products						
Vagifem® vaginal	vaginal tablet	estradiol (as hemihydrate)	10 mcg per tablet	24	51303	€10.32
Vagirux® vaginal	vaginal tablet	estradiol (as hemihydrate)	10 mcg per tablet	24	34449	€10.32
Imvaggis®	vaginal pessary	estriol	30 mcg per pessary	various	Not reimbursed	
Ovestin®	vaginal cream	estriol	0.5 mg per dose (0.1% w/w)	15 g	Not reimbursed	

Abbreviations: g: grams; mg: milligram; mcg: microgram. **Note:** all products with a reimbursement code are available under the DP scheme (maximum of €80 per month)/GMS (€1.50/€1.00 per item) (correct as of September 2022). Refer to individual SmPCs (www.hpra.ie) for further details.

8. Choosing HRT

The type of HRT prescribed will depend on a number of factors including:

1. The benefit/risk of HRT type for the individual
2. If the individual is in the perimenopause or postmenopause phase
3. Whether or not the individual has had a hysterectomy
4. Patient choice
5. Cost
6. Availability of HRT

Professional organisations in other jurisdictions have published recommendations relating to the use of HRT, including guidance on shortages.

In 2020, the BMS and Women's Health Concern (UK) published a consensus statement outlining recommendations on HRT in menopausal women.[7]

The BMS, Royal College of Obstetricians and Gynaecologists (RCOG) and Society of Endocrinology subsequently published a joint position statement in 2022 to highlight a number of best practice recommendations relating to menopause.[8]

The following points and recommendations from the joint position statement (2022) are of note when choosing HRT for individuals:

- Transdermal administration of estradiol is unlikely to increase the risk of venous thrombosis or stroke above that in non-users and is associated with a lower risk compared with oral administration of estradiol.[8]

    - The transdermal route should therefore be considered as the first choice route of estradiol administration in individuals with related risk factors.[8]

- Current evidence suggests that oestrogen alone HRT is associated with a lower risk of breast cancer than combined HRT.[8,59] Breast cancer risk is duration dependent and may vary with the type of progestogen used. The risk of breast cancer should be considered in the context of the overall benefits and risks associated with HRT intake.[8]

    - People with premature ovarian insufficiency (POI) and early menopause (40–45 years old) should be advised that HRT is unlikely to increase risk of breast cancer in younger menopausal individuals under the age of 50.[8]

    - A history of breast cancer should be considered a contraindication to systemic HRT.[8]

- HRT has been shown to have an effective role in the prevention and treatment of osteoporosis.[8,60,61]

    - HRT may be considered as an additional alternative option to bisphosphonates, particularly in younger postmenopausal individuals with menopausal symptoms who are at increased risk of fractures.[8]

    - HRT is considered as first-line intervention for the prevention and treatment of osteoporosis in individuals with POI and early menopause (40-45 years old).[8]

- Evidence from Cochrane database analysis suggests that HRT started before the age of 60 or within 10 years of menopause may result in a reduction in atherosclerosis progression, coronary heart disease and may lower cardiovascular and all-cause mortality.[8,62]

The joint position paper also states that:

- Individuals should be reassured that HRT is unlikely to increase the risk of dementia or to have a detrimental effect on cognitive function in people initiating HRT before the age of 65.[8]

- For most individuals, initiating HRT has a favorable benefit/risk profile. However, HRT should not be used without a clear indication and should not be used for the sole purpose of disease prevention.[8]

- The decision whether to take HRT, the dose and duration of its use should be made on an individual basis after discussing the benefits and risks with each individual. This should be considered in the context of the overall benefits obtained from using HRT, including symptom control and improving quality of life as well as considering the bone and cardiovascular benefits associated with HRT use.[8]

- No arbitrary limits should be set on age or duration of HRT intake.[8]

For more information on the management of menopause refer to the National Medicines Information Centre (NMIC) *Update on the Management of the Menopause* (2017) (expected to be updated in 2023) available on www.nmic.ie.[10]

While the transdermal route of estradiol has been shown to be associated with reduced VTE risk compared to oral formulations of HRT,[3,6-8,15] supply issues with transdermal patches have been ongoing in Ireland (and other countries) for a number of years.[10-12] Therefore, alternative options may need to be considered.

Practice points

- ✓ **The decision whether to take HRT, the dose and duration of its use should be made on an INDIVIDUALISED BASIS after discussing the BENEFITS and RISKS with each patient.**
- ✓ **If a change to the route of administration is being considered, discussion of risk factors and individual preference must also be undertaken.**
- ✓ **COMPLIANCE with individual formulations of oestrogen and progesterone components of HRT is important and this point should be emphasised and discussed with each patient when agreeing on an alternative administration regimen.**

9. MMP switching recommendations for HRT

This document has considered HRT medicinal products authorised and currently marketed in Ireland for the management of menopausal symptoms.

In response to the shortage of HRT transdermal patches, an algorithm to support prescribers in choosing alternative treatments has been developed and is outlined in Section 9.1. This algorithm and a summary of medicinal products for HRT are also available in a printable format, *Tips and Tools for prescribing HRT products*:

https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/prescribing-tips-and-tools/

When prescribing HRT medicinal products for new patients, do not initiate transdermal patches when a supply issue exists. Refer to the dedicated *Medicinal Product Shortages* section of the HPRA website for up to date information on medicinal product shortages:

https://www.hpra.ie/homepage/medicines/medicines-information/medicines-shortages

9.1 MMP recommendations in response to HRT product shortages

Practice points:

- ✓ The decision whether to take hormone replacement therapy (HRT), the dose and duration of its use should be made on an **individualised basis** after discussing the **benefits** and **risks** with each patient.[1]
- ✓ The **transdermal route of administration** should be considered as the preferred route for oestrogen in individuals with risk factors for venous thrombosis or stroke.[1]
- ✓ To maintain continuity of supply for new patients do not initiate transdermal patches that are in short supply. Refer to the *Medicinal Product Shortages* section of the HPRA website, available at: http://www.hpra.ie/homepage/medicines/medicines-information/medicines-shortages

Scenario 1: Oestrogen alone

Individual with hysterectomy currently on an oestrogen alone patch (where supply cannot be maintained)

Step 1: Check for the availability of an alternative oestrogen alone patch
Step 2: Check for the availability of an exempt medicinal product (EMP) alternative patch
IF NO SUPPLY OF A TRANSDERMAL PATCH IS AVAILABLE, CONSIDER ALTERNATIVES BASED ON INDIVIDUAL PATIENT FACTORS USING PATHWAYS OUTLINED BELOW
Consider confirming availability with local pharmacy before prescribing alternatives

Scenario 1: Preferred pathway

Step 3: Change to an alternative oestrogen alone transdermal formulation **(e.g. Divigel® 0.1%, Oestrogel® actuation gel or Lenzetto® transdermal spray)**

Give directions on application

Refer to the table overleaf and the individual Summary of Product Characteristics (SmPC)

Scenario 1: Alternative pathway

Step 3: Assess venous thromboembolism (VTE) and other risk factors, and if appropriate move to step 4
Step 4: Change to an oestrogen alone oral tablet **(e.g. Fematab® or Estrofem®)**

Give directions on use and counsel about increased risk of VTE
Refer to the table overleaf and the individual SmPC

Scenario 2: Continuous combined

Individual with an intact uterus currently on a continuous combined transdermal patch (where supply cannot be maintained)

Step 1: Check for the availability of an EMP alternative patch
IF NO SUPPLY OF A TRANSDERMAL PATCH IS AVAILABLE, CONSIDER ALTERNATIVES BASED ON INDIVIDUAL PATIENT FACTORS USING PATHWAYS OUTLINED BELOW
Consider confirming availability with local pharmacy before prescribing alternatives

Scenario 2: Preferred pathway

Step 2: Change to an alternative oestrogen alone transdermal formulation **(e.g. Divigel® 0.1%, Oestrogel® actuation gel or Lenzetto® transdermal spray)**

AND

Step 3: Add progestogen as:

- Micronised progesterone **(Utrogestan® oral capsule)** 100 mg daily at night*†

Or

- Levonorgestrel intrauterine system (LNG-IUS) 52 mg **(Mirena® IUS)**

Give directions on use
Refer to the table overleaf and the individual SmPC for product information.

*Utrogestan® 100 mg: authorised product is not marketed in Ireland but an EMP alternative is available.

Scenario 2: Alternative pathway

Step 2: Assess VTE and other risk factors, and if appropriate move to step 3
Step 3: Change to a continuous combined HRT oral tablet

Give directions on use and counsel about increased risk of VTE
Refer to the table overleaf and the individual SmPC

†*When using oral progesterone to compliment transdermal oestrogen delivery, ensure that the patient is fully aware of the importance of **compliance** with the progestogen component for safety and to reduce cancer risks.*

- *Continuous use of oral micronised progesterone in this way is not authorised for use in HRT, however micronised progesterone 100 mg (Utrogestan®) is licensed in the UK for use for 25 days per 28-day cycle.*
- *The British Menopause Society (BMS) recommends the use of oral micronised progesterone in this way on a **daily** basis.*[2,3]

Abbreviations: BMS: British Menopause Society; EMP: Exempt medicinal product; HPRA: Health Products Regulatory Authority; HRT: Hormone replacement therapy; LNG-IUS: Levonorgestrel intrauterine system; MMP: Medicines Management Programme; SmPC: Summary of Product Characteristics; VTE: Venous thromboembolism. **References:** 1) Hamoda H, Mukherjee A, Morris E et al. Joint position statement by the British Menopause Society, Royal College of Obstetricians and Gynaecologists and Society for Endocrinology on best practice recommendations for the care of women experiencing the menopause. Post Reproductive Health. 2022; 0(0): 1-3. 2) Hamoda H, Panay N, Pedder H et al. The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women. Post reproductive health. 2020; 26(4): 181-209. 3)The British Menopause Society (BMS). HRT preparations and equivalent alternatives. (2022). Accessed at: https://thebms.org.uk/wp-content/uploads/2022/03/15-BMS-TfC-HRT-preparations-and-equivalent-alternatives-01D.pdf. 4) Summary of Product Characteristics of individual products. Available at: www.hpra.ie and https://products.mhra.gov.uk. Refer to individual SmPCs for further details.

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Appendix A- Prescribing Tips and Tools in response to HRT product shortages

Systemic Medicinal Products for Hormone Replacement Therapy (HRT)[1-4]

Prescribing Tips and Tools in response to HRT product shortages

Practice points:

- ✓ The decision whether to take hormone replacement therapy (HRT), the dose and duration of its use should be made on an **individualised basis** after discussing the **benefits** and **risks** with each patient.[1]
- ✓ The **transdermal route of administration** should be considered as the preferred route for oestrogen in individuals with risk factors for venous thrombosis or stroke.[1]
- ✓ To maintain continuity of supply for new patients do not initiate transdermal patches that are in short supply. Refer to the *Medicinal Product Shortages* section of the HPRA website, available at: http://www.hpra.ie/homepage/medicines/medicines-information/medicines-shortages

Scenario 1: Oestrogen alone

Individual with hysterectomy currently on an oestrogen alone patch (where supply cannot be maintained)

Step 1: Check for the availability of an alternative oestrogen alone patch
Step 2: Check for the availability of an exempt medicinal product (EMP) alternative patch
IF NO SUPPLY OF A TRANSDERMAL PATCH IS AVAILABLE, CONSIDER ALTERNATIVES BASED ON INDIVIDUAL PATIENT FACTORS USING PATHWAYS OUTLINED BELOW
Consider confirming availability with local pharmacy before prescribing alternatives

Scenario 1: Preferred pathway

Step 3: Change to an alternative oestrogen alone transdermal formulation **(e.g. Divigel® 0.1%, Oestrogel® actuation gel or Lenzetto® transdermal spray)**

Give directions on application

Refer to the table overleaf and the individual Summary of Product Characteristics (SmPC)

Scenario 1: Alternative pathway

Step 3: Assess venous thromboembolism (VTE) and other risk factors, and if appropriate move to step 4
Step 4: Change to an oestrogen alone oral tablet **(e.g. Fematab® or Estrofem®)**

Give directions on use and counsel about increased risk of VTE
Refer to the table overleaf and the individual SmPC

Scenario 2: Continuous combined

Individual with an intact uterus currently on a continuous combined transdermal patch (where supply cannot be maintained)

Step 1: Check for the availability of an EMP alternative patch
IF NO SUPPLY OF A TRANSDERMAL PATCH IS AVAILABLE, CONSIDER ALTERNATIVES BASED ON INDIVIDUAL PATIENT FACTORS USING PATHWAYS OUTLINED BELOW
Consider confirming availability with local pharmacy before prescribing alternatives

Scenario 2: Preferred pathway

Step 2: Change to an alternative oestrogen alone transdermal formulation **(e.g. Divigel® 0.1%, Oestrogel® actuation gel or Lenzetto® transdermal spray)**

AND

Step 3: Add progestogen as:

- Micronised progesterone **(Utrogestan® oral capsule)** 100 mg daily at night*†

Or

- Levonorgestrel intrauterine system (LNG-IUS) 52 mg **(Mirena® IUS)**

Give directions on use
Refer to the table overleaf and the individual SmPC for product information.

*Utrogestan® 100 mg: authorised product is not marketed in Ireland but an EMP alternative is available.

Scenario 2: Alternative pathway

Step 2: Assess VTE and other risk factors, and if appropriate move to step 3
Step 3: Change to a continuous combined HRT oral tablet

Give directions on use and counsel about increased risk of VTE
Refer to the table overleaf and the individual SmPC

†*When using oral progesterone to compliment transdermal oestrogen delivery, ensure that the patient is fully aware of the importance of **compliance** with the progestogen component for safety and to reduce cancer risks.*

- *Continuous use of oral micronised progesterone in this way is not authorised for use in HRT, however micronised progesterone 100 mg (Utrogestan®) is licensed in the UK for use for 25 days per 28-day cycle.*
- *The British Menopause Society (BMS) recommends the use of oral micronised progesterone in this way on a **daily** basis.[2,3]*

Abbreviations: BMS: British Menopause Society; EMP: Exempt medicinal product; HPRA: Health Products Regulatory Authority; HRT: Hormone replacement therapy; LNG-IUS: Levonorgestrel intrauterine system; MMP: Medicines Management Programme; SmPC: Summary of Product Characteristics; VTE: Venous thromboembolism. **References:** 1) Hamoda H, Mukherjee A, Morris E et al. Joint position statement by the British Menopause Society, Royal College of Obstetricians and Gynaecologists and Society for Endocrinology on best practice recommendations for the care of women experiencing the menopause. Post Reproductive Health. 2022; 0(0): 1-3. 2) Hamoda H, Panay N, Pedder H et al. The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women. Post reproductive health. 2020; 26(4): 181-209. 3)The British Menopause Society (BMS). HRT preparations and equivalent alternatives. (2022). Accessed at: https://thebms.org.uk/wp-content/uploads/2022/03/15-BMS-TfC-HRT-preparations-and-equivalent-alternatives-01D.pdf. 4) Summary of Product Characteristics of individual products. Available at: www.hpra.ie and https://products.mhra.gov.uk. Refer to individual SmPCs for further details.

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Systemic Medicinal Products for Hormone Replacement Therapy (HRT)[4]

Product	Formulation	Ingredient(s)	Strength	Pack Size	Code(s)[Ω]	Price[Ω]
Oestrogen alone transdermal formulations						
Estradot® transdermal	transdermal patch	estradiol (as hemihydrate)	37.5 mcg per 24 hours	8	68314	€6.03
Evorel® 50	transdermal patch	estradiol (as hemihydrate)	50 mcg per 24 hours	8	24425	€5.21
Estradot® transdermal	transdermal patch	estradiol (as hemihydrate)	50 mcg per 24 hours	8	57226	€6.47
Estradot® transdermal	transdermal patch	estradiol (as hemihydrate)	75 mcg per 24 hours	8	48323	€7.60
Estradot® transdermal	transdermal patch	estradiol (as hemihydrate)	100 mcg per 24 hours	8	47415	€7.65
Oestrogel® actuation gel	transdermal gel	estradiol (as hemihydrate)	750 mcg per pump actuation (0.06% w/w)	80 g (64-doses)	24550	€5.80
Divigel® 0.1 %	transdermal gel	estradiol (as hemihydrate)	1 mg per sachet (0.1% w/w)	28	21272	€9.33
Lenzetto® transdermal	transdermal spray	estradiol (as hemihydrate)	1.53 mg per spray	6.5 ml (56 sprays)	78085	€8.52
Oestrogen alone oral tablet						
Fematab®	oral tablet	estradiol (as hemihydrate)	1 mg	28	24547	€1.38
Fematab®	oral tablet	estradiol (as hemihydrate)	2 mg	28	24536	€2.80
Estrofem®	oral tablet	estradiol (as hemihydrate)	2 mg	28	23655	€4.52
Premarin®	oral tablet	conjugated oestrogens	0.625 mg	28	62063	€2.69
Premarin®	oral tablet	conjugated oestrogens	1.25 mg	28	62071	€3.18
Progestogen alone oral formulations						
Provera®	oral tablet	medroxyprogesterone acetate[¥]	10 mg	90	43645	€19.32
Duphaston®	oral tablet	dydrogesterone	10 mg	42	22818	€8.81
Utrogestan®*	oral capsule (EMP)	micronised progesterone	100 mg	30	20237	Refer to PCRS circular 40/16 (www.pcrs.ie)
Utrogestan®**	oral capsule (EMP)	micronised progesterone	200 mg	15	20238	
Progestogen alone intrauterine system						
Mirena® IUS	LNG-IUS	levonorgestrel	52 mg	1	33578	€116.50 (5 years)
Sequential (cyclical) HRT oral tablet						
Novofem®	oral tablet	estradiol (as hemihydrate) norethisterone acetate	1 mg estradiol (16 days) 1 mg estradiol/1 mg norethisterone acetate (12 days)	84	15628	€14.77
Trisequens®	oral tablet	estradiol (as hemihydrate) norethisterone acetate	2 mg estradiol (12 days), 2 mg estradiol/1 mg norethisterone acetate (10 days), 1 mg estradiol (6 days)	28	48844	€4.96
Femoston®	oral tablet	estradiol (as hemihydrate) dydrogesterone	1 mg estradiol (14 days) 1 mg estradiol/10 mg dydrogesterone (14 days)	28	34236	€5.82
Femoston®	oral tablet	estradiol (as hemihydrate) dydrogesterone	2 mg estradiol (14 days) 2 mg estradiol/10 mg dydrogesterone (14 days)	28	24143	€5.82
Continuous combined HRT transdermal formulations						
Evorel Conti®	transdermal patch	estradiol (as hemihydrate)/norethisterone acetate	50 mcg estradiol/170 mcg norethisterone acetate per 24 hours	8	24560	€13.54
Continuous combined HRT oral tablet						
Kliogest®	oral tablet	estradiol (as hemihydrate)/norethisterone acetate	2 mg estradiol/1 mg norethisterone acetate	28	31283	€6.21
Activelle®	oral tablet	estradiol (as hemihydrate)/norethisterone acetate	1 mg estradiol/0.5 mg norethisterone acetate	28	10454	€7.57
Angeliq®	oral tablet	estradiol (as hemihydrate)/drospirenone	1 mg estradiol/2 mg drospirenone	84	12463	€39.15
Indivina®	oral tablet	estradiol valerate/medroxyprogesterone acetate	1 mg estradiol valerate/2.5 mg medroxyprogesterone acetate	28 84	29020 29032	€8.31 €24.92
Indivina®	oral tablet	estradiol valerate/medroxyprogesterone acetate	1 mg estradiol valerate/ 5 mg medroxyprogesterone acetate	84	29054	€24.92
Indivina®	oral tablet	estradiol valerate/medroxyprogesterone acetate	2 mg estradiol valerate/ 5 mg medroxyprogesterone acetate	84	29096	€24.92
Femoston Conti®	oral tablet	estradiol (as hemihydrate)/dydrogesterone	0.5 mg estradiol/2.5 mg dydrogesterone	84	36925	€24.40
Femoston Conti®	oral tablet	estradiol (as hemihydrate)/dydrogesterone	1 mg estradiol/5 mg dydrogesterone	28	24164	€7.86

Abbreviations: EMP: Exempt medicinal product; g: grams; HRT: Hormone replacement therapy; IUS: intrauterine system; mg: milligram; mcg: microgram; ml: millilitre; LNG-IUS: levonorgestrel-intrauterine system; PCRS: Primary Care Reimbursement Service. **Note:** all products with a code are available under the Drugs Payment Scheme (maximum of €80 per month)/General Medical Services (€1.50/€1.00 per item) (correct as of September 2022). Costs are correct as of September 2022. Refer to individual Summary of Product Characteristics (www.hpra.ie) and the full *HRT Prescribing guidance in response to product shortages* for further details including local (vaginal) oestrogen preparations. *Authorised product is not marketed in Ireland but an EMP alternative is available. **Not authorised in Ireland but available as an EMP. [Ω]As reimbursement code and price. [¥] Medroxyprogesterone acetate 5 mg available as an EMP (not reimbursed).

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