Medicines Management Programme

Medicinal products for hormone replacement therapy (HRT)

Prescribing guidance in response to product shortages

Medicines Management Programme

Prescribing and Cost Guidance

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Abbreviations:

BMS	British Menopause Society
CDS	Community Drug Schemes
CEE	Conjugated equine estrogen
CVD	Cardiovascular Disease
DP	Drug Payment (scheme)
EMP	Exempt Medicinal Product
GMS	General Medical Services
HPRA	Health Products Regulatory Authority
HRT	Hormone Replacement Therapy
IMS	International Menopause Society
LGN-IUS	Levonorgestrel intrauterine system
MMP	Medicines Management Programme
NICE	National Institute for Health and Care Excellence
NMIC	National Medicines Information Centre
PCERS	Primary Care Eligibility and Reimbursement Service
VTE	Venous thromboembolism

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1. Background

1.1 Brief summary of menopause

The menopause, which is caused by ovarian failure resulting in oestrogen deficiency, occurs in most women at an average age of 51-52 years (range from 45 to 55 years).[1,2] Definitions which describe the menopause include: 1) **perimenopause** (also known as the menopausal transition) - the time during which the woman experiences symptoms and cycle variability until 12 months after the final menstrual period and 2) **postmenopause** - the time after menopause has occurred, starting when a woman has not had a menstrual period for 12 months.[3] Symptoms occurring during the menopause include irregular bleeding, vasomotor symptoms (e.g. hot flushes and night sweats) and vulvovaginal atrophy.[1,3]

Hormone replacement therapy (HRT) remains the most effective therapy for relieving vasomotor symptoms and vulvovaginal atrophy.[1] Women with vasomotor symptoms require systemic HRT while women who have vulvovaginal atrophy only, require local oestrogen.[5] HRT also reduces the risk of osteoporosis and may be beneficial for other menopausal symptoms such as joint and muscle pains, mood changes and sleep disturbances.[1,3,6]

There are various preparations and formulations of HRT, which contain different oestrogens and progestogens. Risks associated with use of HRT include:

- venous thromboembolism (VTE) (especially in the first year of use and with oral formulations)
- breast cancer (increased risk with oestrogen and progestogen combination)
- stroke (increased risk with oral HRT)
- endometrial cancer (increased risk with unopposed oestrogen)
- ovarian cancer.[3-11]

There have been concerns regarding an increased risk of cardiovascular disease (CVD) associated with HRT,[8,9] however current evidence suggests that HRT does not increase the risk of CVD when started in women aged <60 years.[3] In the majority of women the benefits of short-term HRT for the treatment of menopausal symptoms outweigh the risks, especially in those aged <60 years.[5]

Tibolone is a synthetic steroid that has oestrogenic, progestogenic and weak androgenic activity; it is less effective than oestrogen therapy in reducing vasomotor symptoms.[6] Tibolone is associated with an increased risk of breast cancer, stroke and endometrial cancer.[5]

The decision to prescribe HRT and the choice of HRT for an individual patient depends on a number of factors including the patient's risk factors for adverse effects (e.g. VTE, breast cancer, endometrial cancer and CVD), the patient's choice, cost and availability of the HRT.[4,7] For more information on the management of menopause refer to the National Medicines Information Centre (NMIC) "Update on the Management of the Menopause" (2017) available on www.nmic.ie.[12]

1.2 Availability of hormone replacement therapy (HRT)

Shortages of medicinal products containing HRT have been reported in a number of countries over the past year, including Ireland. The Health Products Regulatory Authority (HPRA) monitors and reports on such medicine shortages and updates information as it becomes available. Suppliers have stated that recent shortages relate to both active substance availability and manufacturing delays.[13] These shortages may result in short periods of intermittent supply issues or more prolonged periods where products are unavailable. This document was developed due to supply issues relating to transdermal HRT patches.

During supply disruptions, alternative treatments are available to meet patients' needs however there may be a requirement to use a different route/process of administration or to use two medicinal products rather than one (i.e. oestrogen and progestogen as separate products rather than one combination product). Switching a patient between products (due to supply issues) must involve a discussion with the patient, 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 Drug Payment (DP) schemes, they must have a reimbursement code. Some HRT therapies are available in Ireland where the market authorisation holders have not applied for reimbursement under the CDS and therefore these therapies are only available for patients to purchase privately on prescription. This should also be considered when choosing a HRT regimen for individual patients. Where a product has a reimbursement code it is listed in the tables below along with the Primary Care Eligibility and Reimbursement Service (PCERS) reimbursed price (available on www.pcrs.ie).

Enquiries to the NMIC from prescribers about HRT product shortages and alternative options for patients when medicines are in short supply have increased in the last 12 months highlighting the requirement for more information and support for GPs in this area.

2. Scope

The MMP has developed this document to outline the different types of HRT treatments currently available in Ireland and offer suggestions for alternatives where supply issues exist.

3. Hormone Replacement Therapy (HRT)

Women with an intact uterus require a combination of oestrogen and progestogen (combined HRT) to reduce the risk of endometrial hyperplasia, while women who have had a hysterectomy only require oestrogen.[1,3,5] Combined HRT can be further sub-divided into sequential (or cyclical) HRT and continuous combined HRT (see section 2.3 below for further detail). Table 1 summarises HRT regimens. Currently marketed HRT preparations will be described in more detail in the following sections.

Table 1: Systemic hormonal therapy regimens [2,12]

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

*LNG-IUS: levonorgestrel intra-uterine system

3.1 Formulations of HRT

Oestrogen alone and combined HRT are available in a variety of preparations with different routes of administration and different associated risk factors.

3.1.1 Transdermal patches

Transdermal patches may contain oestrogen alone or a combination of oestrogen and progestogen (combined HRT). There is a lower risk of VTE associated with the transdermal route than with oral formulations.[2-5,10] The patches are applied to any area below the waist[14,15] or abdomen[16-19] and should not be applied to the breasts.[14-19]

3.1.2 Oral tablets

A wide range of oral tablets are available, which are taken once a day. They may contain oestrogen alone or a combination of oestrogen and progestogen (combined HRT) as either continuous or sequential HRT.

3.1.3 Transdermal gel

Oestrogen 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[20] or upper arm, shoulder or inner thigh.[21] It should not be applied on or near the breasts.[20,21]

3.1.4 Local HRT

Vaginal oestrogen (local HRT) preparations including vaginal creams, vaginal tablets or vaginal pessaries contain a small amount of oestrogen; it is indicated for local symptoms, such as vaginal dryness and urinary symptoms.[5] Local HRT will not improve other symptoms, such as hot flushes, or protect against the longer term effects of the menopause such as osteoporosis. The risks that are associated with systemic HRT have not been identified with local low-dose oestrogen therapy.[7]

Different formulations for individual types of HRT that are available in Ireland are outlined in tables 2 to 4 below.

3.2 Oestrogen alone HRT

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

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

- Transdermal patches
- Oral tablets
- Transdermal gel preparations
- Local (vaginal) application

Table 2 outlines systemic oestrogen containing medicinal products authorised in Ireland and associated formulations and costs.

Table 2: Systemic oestrogen alone medicinal products authorised in Ireland [14,16-26]

Product	Dose and type of oestrogen	Formulation	Reimbursed code (s)	Reimbursed price* (quantity)
Evorel®	50mcg estradiol	Transdermal patch	24425	€5.21
Estradot®	37.5mcg 50mcg 75mcg 100mcg estradiol hemihydrate	Transdermal patch	68314 57226 48323 47415	€6.03 €6.47 €7.60 €7.65
Fematab®	1mg 2mg estradiol hemihydrate	Oral tablet	24547 24536	€1.38 €2.80
Estrofem®	2mg estradiol hemihydrate	Oral tablet	23655	€4.52
Premarin®	0.625mg 1.25mg conjugated estrogens	Oral tablet	62063 (74103) 62071 (74104)	€2.69 (28) €7.64 (84) €3.18 (28) €9.24 (84)
Divigel®	0.1% gel – 1mg estradiol hemihydrate	Transdermal gel	21272	€9.33
Oestrogel®	Pump-pack 750mcg gel Estradiol	Transdermal gel		Due to be added to the reimbursed list in Sept/Oct 2020

Refer to individual SmPCs (www.hpra.ie) for further details

* Prices listed are correct as of July 2020 (www.pcrs.ie)

Climara® and Climara Forte® transdermal patches are still listed on the PCERS list of reimbursed items however they are no longer marketed by the company in Ireland.

3.3 Progestogens

Progestogens are indicated as an adjunct to oestrogens in postmenopausal women with an intact uterus.[1-3,5,7] A variety of progestogens in differing strengths are available in progestogen alone preparations (table 3) and as combination products (tables 4 and 5).

Combination products outlined in section 2.4 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 gel (table 2) and oral or intrauterine progestogen products could be considered (table 3).

Oral medroxyprogesterone is authorised for adjunctive use in HRT at a dose of 10mg daily for 10-12 days beginning on day 16 of a 28 day course of oestrogen therapy.[27] The standard oral dose of dydrogesterone is 10mg daily for the last 14 days of each 28 day oestrogen treatment cycle, in women on sequential HRT.[28] Progestogen as a 52mg levonorgestrel intrauterine system (LNG-IUS) is also indicated for protection from endometrial hyperplasia during oestrogen replacement therapy.[29]

Micronised progesterone has been found to have a more selective effect on progesterone receptors and results in less interaction with androgenic and mineral-corticoid receptors compared with other progestogens.[4] 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.[30-32] It is authorised as HRT in other countries (including the UK).[33] Utrogestan® (micronised progesterone) 200mg and 100mg oral capsules are currently not authorised in Ireland but are available as Exempt Medicinal Products (EMP).* The oral dose of Utrogestan® is 200mg daily for 12 days from day 15 to day 26 for sequential HRT therapy or 100mg daily from day 1 to day 25.[33] Oral micronised progesterone 100mg **daily** (at night) is often used as the progesterone component of continuous combined HRT and is recommended by organisations including the International Menopause Society (IMS) and the British Menopause Society (BMS). [7,34]

*For further information on Exempt Medicinal Products please refer to the HPRA website on: http://www.hpra.ie/homepage/medicines/regulatory-information/medicines-authorisation/notification-system-for-exempt-(unauthorised)-products

Table 3 outlines progestogen only medicinal products available in Ireland and associated formulations and cost.

Table 3: Progestogen only medicinal products available in Ireland [27-29,33]

Product(s)	Dose and type of progestogen	Formulation	Reimbursed code	Reimbursed price* (quantity)
Provera®	10mg medroxyprogesterone acetate	Oral tablet	43645	€19.32 (90)
Duphaston®	10mg dydrogesterone	Oral tablet	22818	€8.81 (42)
Mirena®	52mg levonorgestrel	LNG-IUS	33578	€116.50 (5 years)
Utrogestan® ****	100mg 200mg micronised progesterone	Oral capsule	20237 (EMP) 20238 (EMP)	Refer to PCERS circular 39/16 (www.pcrs.ie)

Refer to individual SmPCs (www.hpra.ie) for further details

*Prices listed are correct as of July 2020 (www.pcrs.ie)

**Not authorised in Ireland but available as an Exempt Medicinal Product (EMP)

3.4 Combined HRT

Combined HRT (oestrogen and progestogen) is necessary for women with an intact uterus who require HRT, either as sequential (cyclical) HRT or continuous combined HRT.[7] Continuous combined HRT is indicated for postmenopausal women, more than 12 months since their last menstrual period.[5]

3.4.1 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 women who are perimenopausal or in the early postmenopause.[6] Women taking sequential HRT have a monthly withdrawal bleed which is often light. [6] Sequential HRT medicinal products are available only as oral tablets in Ireland (table 4). To achieve sequential HRT with other formulations, women could use oestrogen transdermal patch or gel with an oral progestogen (e.g. dydrogesterone 10mg daily for the last 14 days, medroxyprogesterone 10mg daily from day 16 for 10 to 12 days or micronised progesterone [Utrogestan® 200mg EMP] 200mg daily for 12 days from day 15 to 26 of a 28 day cycle).[4,27,28,33] See tables 2 and 3 for individual product details.

Table 4 outlines sequential HRT medicinal products authorised in Ireland and associated formulations and cost.

Table 4: Sequential (cyclical) HRT medicinal products authorised in Ireland [35-38]

Product	Dose and type of oestrogen/progestogen	Formulation	Reimbursed code	Reimbursed price* (quantity)
Novofem®	1mg estradiol (16 days) 1mg estradiol/1mg norethisterone (12 days)	Oral tablet	15628	€16.12 (2x28)
Trisequens®	2mg estradiol (12 days) 2mg estradiol/1mg norethisterone (10 days) 1mg estradiol (6 days)	Oral tablet	48844	€4.96 (28)
Femoston®	1mg estradiol (14 days) 1mg estradiol/10mg dydrogesterone (14 days) 2mg estradiol (14 days) 2mg estradiol/10mg dydrogesterone (14 days)	Oral tablet	34236 24143	€5.82 (28) €5.82 (28)

Refer to individual SmPCs (www.hpra.ie) for further details

*Prices listed are correct as of July 2020 (www.pcrs.ie)

3.4.2 Continuous combined HRT

Continuous combined HRT is an option for postmenopausal women from 12 months after their last menstrual period.[5] 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 women have no bleeding on continuous combined HRT after 12 months.[2] Table 5 outlines continuous combined HRT medicinal products authorised in Ireland and associated formulations and cost.

Table 5: Continuous combined HRT medicinal products authorised in Ireland [15, 39-46]

Product	Dose and type of oestrogen/progestogen	Formulation	Reimbursed code	Reimbursed price* (quantity)
Evorel Conti®	50mcg estradiol hemihydrate/170mcg norethisterone acetate	Transdermal patch	24560	€13.54
Kliogest®	2mg estradiol/1mg norethisterone	Oral tablet	31283	€6.21 (28)
Activelle®	1mg estradiol hemihydrate/0.5mg norethisterone	Oral tablet	10437 10454 10631	€7.38 (28) €7.60 (28) €7.38 (28)
Angeliq®	1mg estradiol hemihydrate/2mg drospirenone	Oral tablet	12463	€39.57 (84)
Indivina®	1mg/2.5mg 1mg/2.5mg 1mg/5mg 2mg/5mg Estradiol valerate/ medroxyprogesterone	Oral tablet	29020 29032 29054 29096	€8.36 (28) €28.50 (84) €25.08 (84) €25.08 (84)
Femoston Conti®	0.5mg /2.5mg 1mg /5mg estradiol hemihydrate/dydrogesterone	Oral tablet	36925 24164	€24.40 (84) €7.94 (28)

Refer to individual SmPCs (www.hpra.ie) for further details

*Prices listed are correct as of July 2020 (www.pcrs.ie)

At the time of this publication there were supply issues for transdermal (and some oral) continuous combined HRT. To achieve continuous combined HRT with alternative formulations women could use oestrogen alone as an oestrogen transdermal patch or as oestrogen transdermal gel (table 2) **and** a progestogen IUS or oral progestogen (table 3). Oral progestogens are not authorised for continuous use in this way however daily use of oral progestogens is recommended by some organisations including the IMS and the BMS.[7,34] The BMS recommends the following unauthorised options " Micronised Progesterone: Utrogestan® 100 mg orally at night daily on a continuous basis or Provera® (medroxyprogesterone) 5 mg orally daily on a continuous basis." [34]

See tables 2 and 3 for individual product details.

3.5 Tibolone

Tibolone, a synthetic form of 'period-free' HRT, is another option for women in the postmenopausal phase, with either an intact uterus or hysterectomy.[47]

3.6 Local (vaginal) oestrogen

Table 6 outlines local HRT medicinal products (oestrogen containing) authorised in Ireland and associated formulations and cost.

Table 6: Local HRT medicinal products authorised in Ireland [48-50]

Product	Dose and formulation	Reimbursed code	Reimbursed price (quantity)
Vagifem®	10mcg estradiol vaginal tablets	51303	€20.65 (24)
Ovestin®	1mg/gram (0.5mg per dose) estriol cream	No code	No reimbursed price
Imvaggis®	0.03mg estriol waxy pessary	No code	No reimbursed price

Refer to individual SmPCs (www.hpra.ie) for further details

*Prices listed are correct as of July 2020 (www.pcrs.ie)

4. 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 perimenopausal or postmenopausal
3. Whether or not the individual has had a hysterectomy
4. Patient choice
5. Cost and availability of HRT

The transdermal route has been shown to be associated with reduced VTE risk compared to oral formulations of HRT, [3-5,10] however as previously discussed, supply issues with transdermal patches have been ongoing in Ireland (and other countries) for a number of months.[12]

The oestrogen alone and continuous combined transdermal patches remain in short supply.[13] Transdermal patches for sequential HRT are also not available in Ireland.

For women requiring either "oestrogen alone" (following hysterectomy) or combined HRT **and** if there is a preference for the transdermal route, alternatives must be considered, including:

- Oestrogen gel for oestrogen alone therapy
- Oestrogen gel and 12-14 days of an oral progestogen for sequential therapy - compliance is very important
- Oestrogen gel and progestogen administered as the 52mg levonorgestrel intra-uterine system (LNG-IUS) (Mirena®) for continuous combined therapy
- Oestrogen gel and continuous daily oral progestogen (preferably as micronised progesterone) for continuous combined therapy (off label use but recommended by BMS and recognised internationally) – compliance is very important

5. HRT switching recommendations

The HSE-Medicines Management Programme, in collaboration with Dr Deirdre Lundy (GP specialist in reproductive health, ICGP) and the NMIC has produced an algorithm for alternative choices in response to a shortage of HRT transdermal patches to support prescribers in choosing alternative treatments. See Appendix A for printable version.

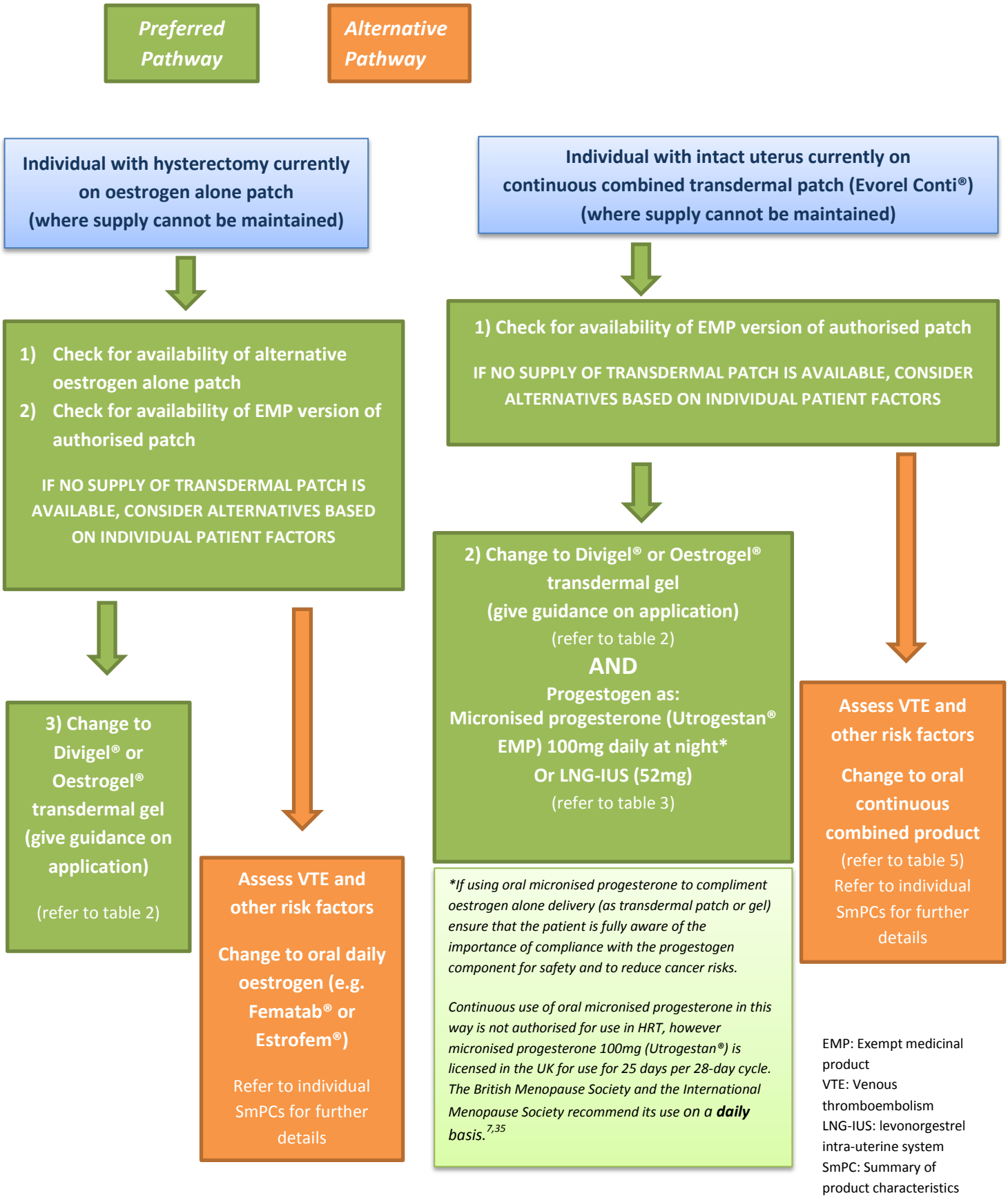
When prescribing HRT treatment for new patients do not initiate transdermal patches when a supply issue exists. Updates on product shortages can be found here: HPRA Shortages Webpage

Current transdermal products which have experienced shortages include:

- ***Evorel® and Estradot® range (oestrogen alone forms of systemic transdermal HRT)***
- ***Evorel Conti® (continuous combined form of systemic transdermal HRT)***

Discuss all changes and agree with the individual patient, including discussion about risk profiles and the importance of compliance when prescribing two separate treatments.

5.1 Algorithm for changing from transdermal patches



EMP: Exempt medicinal product
VTE: Venous thromboembolism
LNG-IUS: levonorgestrel intra-uterine system
SmPC: Summary of product characteristics

5.2 Practice points

VTE Risk

Use of oral HRT has been associated with a significantly increased risk of venous thromboembolism (VTE) compared to no exposure.

Transdermal HRT is associated with a lower risk of VTE than oral formulations

If a change to the route of administration is being considered, discussion of risk factors and patient preference must be undertaken

Product supply and compliance with new regimen

✔ **If transdermal patches (oestrogen alone and/or combined with a progestogen) are in short supply, consider firstly if an alternative transdermal patch is available (either as EMP of authorised medicine or as alternative authorised medicine) and failing this, consider an alternative preparation in the form of transdermal gel for the oestrogen component and where indicated a separate progestogen (oral micronised progesterone or 52mg LNG-IUS) for women with an intact uterus.**

✖ **To maintain continuity of supply for new patients do not initiate transdermal patches that are in short supply. See:** HPRA Shortages Webpage

Contact community pharmacy prior to repeating prescription for transdermal patches while the shortage is in place. If no supply is available, discuss alternatives with patient in terms of risk-benefit ratio and the importance of compliance with chosen regimen.

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