

1 **Prescribing Hormonal Replacement Therapy: Key considerations for**
2 **Primary Care Physicians**

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1 The last few years has seen a dramatic rise in the number of women seeking advice for the
2 menopause and Hormone Replacement Therapy (HRT)¹. Navigating the complexities of
3 HRT and being able to discuss the options available in primary care is therefore, essential.
4 The aim of this article is to provide key considerations for Primary Care Physicians (PCPs)
5 when considering HRT implementation and also the role of testosterone and vaginal estrogen
6 for symptom management (Figure 1- Flowchart of key considerations when commencing
7 HRT). It is beyond the scope of this article to discuss the role of Tibolone, Selective Estrogen
8 Modulators (SERM) and DHEA for managing menopausal symptoms and PCPs would be
9 encouraged to seek specialist input prior to commencing these treatments.

11 **Key Consideration 1: Is HRT appropriate?**

12 Although hot flushes and night sweats are commonly associated with menopause, a wide
13 plethora of symptoms including, brain fog, insomnia, reduced libido have been reported².
14 Although HRT has been shown to be beneficial for symptomatic women who are peri-
15 menopausal (Last Menstrual Period (LMP) within last 12months) or menopausal (more than
16 12months since last LMP), a holistic review of lifestyle factors and exploring natural or
17 herbal therapies is crucial prior to its implementation. Contraindications to its use include
18 previous or current history of hormone sensitive breast cancer, endometrial cancer and
19 endometrioid ovarian cancers³. Potential alternatives in these cases include Gabapentin,
20 Pregabalin, Clonidine and Venlafaxine and can be started in primary care following a risk
21 versus benefit discussion.

23 **Key consideration 2: What preparation and regime is required?**

24 Once the decision is made to commence HRT, it is important to consider whether a combined
25 estrogen/progesterone or estrogen only preparation is required. For all women with an intact
26 uterus, the former is vital for reducing the risk of endometrial hyperplasia.

28 While combined HRT is available as either a sequential or continuous regime, the
29 preparations vary by the type of progesterone used and dose of estrogen. With the
30 management of menopausal symptoms determined by the latter, prescription is often guided
31 by availability. While both sequential and continuous combined regimes deliver a daily dose
32 of estrogen, sequential regimes deliver progesterone for up to 12days per month (compared to
33 continuous regimes which deliver a daily dose). Sequential regimes are recommended for
34 peri-menopause to reduce the risk of breakthrough bleeding and these women should be

1 counselled that they may experience a withdrawal bleed on their progesterone free days.
2 Generally, women can be switched from a sequential to a continuous regime after two years
3 if they are below the age of 50years or after a year, after the age of 50years.

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5 **Key consideration 3: What is the most appropriate route and dose of HRT to start on?**

6 Once the preparation and regime has been decided, the next step is to choose the route and
7 dose of HRT. With HRT available either as an oral or transdermal preparation, the latter
8 bypasses first pass metabolism of the liver and is suitable for women with a history of
9 Venous Thromboembolism (VTE), liver disease, malabsorptive diseases and migraines⁴.
10 Available as a patch, cream (Estrogel), gel (Sandrena) or spray, Lenzetto, transdermal
11 preparations are also favoured for women with a BMI>30. For those with a BMI>40, referral
12 to a specialist menopause clinic would be recommended.

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14 The patch is available as either estrogen only or as a combined estrogen/progesterone patch,
15 is applied to the thighs and changed on a twice weekly basis. In contrast, Estrogel, Sandrena
16 and Lenzetto are estrogen only and are applied everyday. With the exception of Lenzetto,
17 which is applied on the arms, Estrogel and Sandrena are applied to the thighs. Additional
18 progesterone cover must therefore be prescribed separately for those with an intact uterus and
19 further information on dosage and options for progesterone cover are provided in Table 1
20 (Table 1- Progesterone cover for HRT).

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1 **Table 1- Progesterone cover for HRT**

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Progesterone	Comments	Side effects	Sequential Combined Regime	Continuous Combined Regime
Oral				
Utrogestan	Micronized progesterone, bio-identical and helps with sleep and safe for those with previous history of VTE and migraines	Nausea Fluid retention	200mg for 12days per month, to take at night.	100mg every night
Desogestrel	Contraceptive action. Off-license use and not first-line	Nausea Fluid retention	150mg daily	150mg daily
Medroxyprogesterone	Use with caution with previous history of hormone sensitive breast cancer, VTE and migraines	Mood changes Fluid retention Breast tenderness	10mg daily for 12days per month	2.5mg daily
Norethisterone	Use with caution with previous history of hormone sensitive breast cancer, VTE and migraines	Mood changes Fluid retention Breast tenderness	5mg for 12days per month	5mg daily or consider Noriday 3 tablets daily.
Intrauterine Contraceptive Device				
Mirena	Can remain in situ for 5years (off-license use) for endometrial protection and contraceptive cover.	Irregular or heavy bleeding more commonly seen within first 4months of insertion.	NA	NA

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4 The starting dose of estrogen should be guided by age, with women below the age of 50years
 5 generally requiring high doses compared to women between 50-59years, who may note
 6 alleviation of their symptoms at low or medium doses. It is also advised that HRT should be
 7 commenced for women over the age of 60years or more than 10years from their LMP at low
 8 or ultra-low doses and transdermally⁵. To reduce the risk of oestrogenic side effects (bloating,
 9 breakthrough bleeding, nausea and headache), it is recommended that all women should start
 10 on a lower dose initially and be reviewed at four months and thereafter, at a minimum,
 11 annually to ensure symptom management. While it is beyond the scope of this article to
 12 provide a detailed breakdown of all the different types and doses of HRT available, a

- 1 prescribing guide outlining the estrogen dose equivalence between some of the products
- 2 available is provided in Table 2⁶ (Table 2- Guide for prescribing HRT).

Table 2- Guide for prescribing HRT

HRT	Regime	Estrogen strength			
		Ultra-low	Low	Medium	High
Oral (once a day tablets)	Estrogen only	Alternate days Elleste Solo 1mg or Zumenon 1mg	Elleste Solo 1mg Zumenon 1mg	Elleste Solo 2mg Zumenon 2mg	Elleste Solo 2mg & 1mg Zumenon 2mg & 1mg
	Sequential Combined		Elleste Duet 1mg Femoston 1/10	Elleste Duet 2mg Femoston 2/10	Elleste Duet 2mg & Elleste Solo 1mg
	Continuous Combined	Femoston Conti Low	Femoston Conti Kliovance	Elleste Duet Conti 2mg Kliofem 2mg	Elleste Duet Conti 2mg & Elleste Solo 1mg
Patch (applied on thigh and changed twice weekly)	Estrogen only	½ Evorel 25 patch ½ Estradot 25 patch	Evorel 25 Estradot 25	Evorel 50 Estradot 50	Evorel 75/100 Estradot 75/100
	Sequential Combined	½ Evorel 25/Estradot 25 patch & Utrogestan 200mg for 12days/month	Evorel 25/ Estradot 25 & Utrogestan 200mg for 12days/month	Evorel Sequi Femseven Sequi	Evorel Sequi & Evorel or Estradot 25/50
	Continuous Combined	½ Evorel 25 or Estradot 25 patch Utrogestan 100mg everynight	½ Evorel Conti patch ½ Femseven Conti patch	Evorel Conti Femseven Conti	Evorel Conti & Evorel or Estradot 25/50
Estrogel (daily application to thigh)	Estrogen only	½ pump	1pump	2pumps	3-4 pumps
Sandrena (daily application to thigh)	Estrogen only	½ 0.5mg sachet	0.5mg	1mg	1.5-2mg
Lenzetto (daily spray to arms)	Estrogen only	1 spray	2 sprays	3 sprays	

1 **Key consideration 4: Is testosterone or vaginal estrogen required?**

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3 *Testosterone*

4 Testosterone supplementation on its own is not recommended due to the side effects of
5 bloating, acne and hair growth⁸. While switching women from oral to transdermal HRT can
6 increase the levels of free circulating testosterone, testosterone supplementation is
7 recommended for women who continue to experience low libido and fatigue despite adequate
8 estrogen replacement⁷. Contraindications to its use include active liver disease and hormone
9 sensitive breast cancer. Prior to its implementation, discussion with a specialist menopausal
10 service would be recommended and total testosterone levels should always be checked prior
11 to commencement and again six-twelve months after initialising therapy with the aim of
12 keeping levels within female's physiological range. With testosterone implants becoming
13 increasingly difficult to source, transdermal preparations available in the UK can either be
14 administered on a daily or twice weekly basis. Application should be on the thighs but not
15 over the same area if transdermal HRT is concurrently being used.

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17 *Vaginal estrogen*

18 With vaginal estrogen now available over the counter, its use is recommended for women
19 experiencing genitourinary symptoms such as, vaginal dryness, superficial dyspareunia,
20 vulvovaginal irritation, increased urinary frequency and urgency. Available either as a
21 pessary or a cream, women should be advised to commence on a daily dose for 2weeks
22 before being gradually reduced every 2 weeks and can remain on a lifelong twice weekly or
23 once weekly regime. For women with a previous or current history of breast cancer, input
24 from a specialist menopause service would be recommended prior to commencing vaginal
25 estrogen.

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28 It is recognised that prescribing HRT can be challenging within Primary care. By providing a
29 breakdown of the key considerations, the aim is that this can guide PCPs to be more
30 confident in initialising HRT and seeking specialist input when appropriate.

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35 **Declarations**

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37 *Competing Interests*

38 Rima Chakrabarti is a member of the British Menopause Society (BMS).

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References

- ¹ Quinn, H. HRT prescriptions double in five years, despite supply shortages. *The pharmaceutical journal*. Available from <https://pharmaceutical-journal.com/article/news/hrt-prescriptions-more-than-double-in-five-years-despite-supply-shortages>
Accessed 16th March 2023
- ² Santoro N, Epperson CN, Mathews SB. Menopausal Symptoms and Their Management. *Endocrinol Metab Clin North Am*. 2015 Sep;44(3):497-515. Available from DOI: 10.1016/j.ecl.2015.05.001.
Accessed 16th March 2023
- ³ Harper-Harrison G, Shanahan MM. Hormone Replacement Therapy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK493191/>
- ⁴ Kopper NW, Gudeman J, Thompson DJ. Transdermal hormone therapy in postmenopausal women: a review of metabolic effects and drug delivery technologies. *Drug Des Devel Ther*. 2009; 6;2:193-202. Available from DOI: 10.2147/dddt.s4146.
Accessed 10th February 2023
- ⁵ British Menopause Society (BMS). BMS & WHC's 2020 recommendations on hormone replacement therapy in menopausal women
Available from <https://thebms.org.uk/publications/consensus-statements/bms-whcs-2020-recommendations-on-hormone-replacement-therapy-in-menopausal-women/>
Accessed 16th March 2023
- ⁶ British Menopause Society (BMS). HRT- practical prescribing. 2022
Available from <https://thebms.org.uk/wp-content/uploads/2022/12/03-BMS-TfC-HRT-Practical-Prescribing-NOV2022-A.pdf>
Accessed 11th February 2023
- ⁷ British Menopause Society (BMS). Testosterone replacement in Menopause. 2022
Available from <https://thebms.org.uk/wp-content/uploads/2022/12/08-BMS-TfC-Testosterone-replacement-in-menopause-DEC2022-A.pdf>
Accessed 13th February 2023

Figure 1- Flowchart of key considerations when commencing HRT

